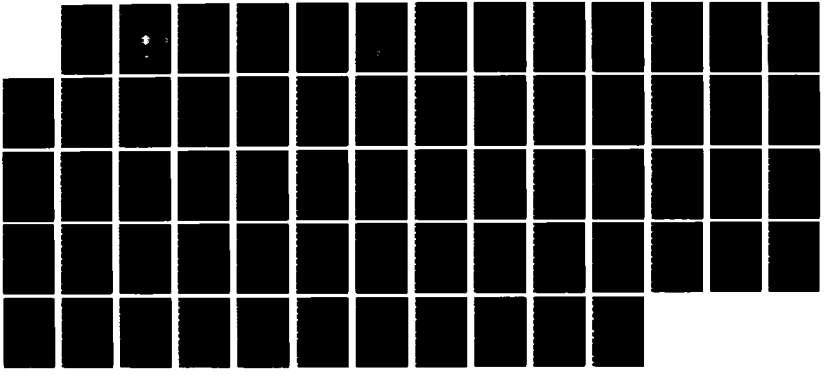
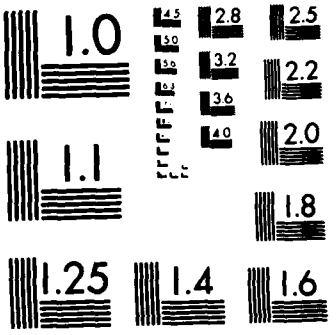
AD-A171 737 KINETICS MODELING OF CANCER IMMUNOLOGY(U) NAVAL ACADEMY 1/1
ANNAPOLIS MD S W HELMERS 09 MAY 86 USNA-TSPR-137

UNCLASSIFIED F/G 6/16 NL





(18)

A TRIDENT SCHOLAR PROJECT REPORT

NO. 137

KINETICS MODELING OF CANCER IMMUNOLOGY

UNITED STATES NAVAL ACADEMY
ANNAPOLIS, MARYLAND
1986

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE	READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER: U.S.N.A. - TSPR; no. 137 (1986)	2. GOVT ACCESSION NO.: AD-A171 237
	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle): KINETICS MODELING OF CANCER IMMUNOLOGY	5. TYPE OF REPORT & PERIOD COVERED: Final: 1985/1986
	6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s): Helmers, Scott Whittaker	8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS: United States Naval Academy, Annapolis.	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS: United States Naval Academy, Annapolis.	12. REPORT DATE: 9 May 1986
	13. NUMBER OF PAGES: 60
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)	15. SECURITY CLASS. (of this report)
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

This document has been approved for public release; its distribution is UNLIMITED.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

This document has been approved for public release; its distribution is UNLIMITED.

18. SUPPLEMENTARY NOTES

Accepted by the U.S. Trident Scholar Committee.

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Antigen-antibody reactions
Antigens
Cancer
Immune response

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

In the presence of antibody, some cancerous antigens have demonstrated a unique mechanism of immunological escape. The mechanism by which these tumors avoid immune destruction is to constantly change their antigen surface, thus preventing the immune system from effectively completing its response to a given antigen. The exact means by which these tumor cells change their antigen surface is unknown. In this study, a kinetics model for an immune response to such a system is presented. Comparisons between the model data and experimental

(OVER)

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

S/N 0102-LF-014-6601

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

data indicate similar response characteristecs, e.g. amplitude, shape and oscillation frequency of the cancer cell populations, thus lending credibility to the mathematical model. In addition, parameters of the model are varied to note the degree of sensitivity of the cancerous system, in order to achieve further meaningful results. Finally, concepts for a more rigorous model, including more intercellular interactions, are proposed.

"Kinetics Modeling of Cancer Immunology"

A Trident Scholar Project Report

by

Midn 1/C Scott Helmers, Class of 1986

United States Naval Academy

Annapolis, Maryland

Boyd A. Waite

Assistant Professor Boyd Waite
Chemistry Department

Accepted for Trident Scholar Committee

Carl Schmidt

Chairman

9 May 1986

Date

Report Control Symbol USNA-1531-2

Abstract

In the presence of antibody, some cancerous antigens have demonstrated a unique mechanism of immunological escape. The mechanism by which these tumors avoid immune destruction is to constantly change their antigen surface, thus preventing the immune system from effectively completing its response to a given antigen. The exact means by which these tumor cells change their antigen surface is unknown. In this study, a kinetics model for an immune response to such a system is presented. Comparisons between the model data and experimental data indicate similar response characteristics, e.g. amplitude, shape, and oscillation frequency of the cancer cell populations, thus lending credibility to the mathematical model. In addition, parameters of the model are varied to note the degree of sensitivity of the cancerous system, in order to achieve further meaningful results. Finally, concepts for a more rigorous model, including more intercellular interactions, are proposed.

Table of Contents

Abstract..... 1

Table of Contents..... 2

Introduction

- General Introduction..... 3
- Introduction to Immunology..... 5
- Cancer Immunology..... 15

Methods..... 27

Results..... 34

Discussion

- Discussion of Model Results..... 39
- Future Modeling Research..... 41

Conclusion..... 46

References..... 47

Appendices

- Computer Program..... 51
- Model Results..... 57

Introduction

General Introduction

Modeling of cancer immunology simply involves the development of a mathematical representation of the human body's immunological response to a cancerous growth.

Models are not uncommon to the field of chemistry, physics, or engineering. In order to perform day-to-day calculations, a scientist must use mathematical models in order to achieve any type of meaningful results. This is true due to the immense complexity of all actual physical systems. For example, in the case of a simple gaseous system, a scientist utilizes the ideal gas law ($PV = nRT$) to approximate the results obtained from a real gas system. Although the intermolecular interactions between the atoms or molecules of any gaseous system are so complex as to prevent the creation of any model which could perfectly explain the results of a gas law experiment, a simple mathematical model such as the ideal gas law can be applied to approximate those results. If the researcher or scientist requires a better approximation of the experimental results, the ideal gas law can be modified or expanded upon to increase its accuracy. An example of this type of expansion of a model is the van der Waal's equation:

$$(P+an^2/V^2)\ (V-nb) = nRT$$

where the a and b terms have been added to account for different types of molecular interactions not included in the ideal gas law. Thus, with the van der Waal's expansion of the ideal gas equation, a more rigorous model is created, yet still a model that is not completely accurate [1].

Similarly, in quantum mechanics, a chemist or physicist uses the equations derived from a hydrogen atom to approximate the quantum mechanical solutions to electron orbitals of both other atoms and of molecules [1]. Although such approximations are not entirely accurate, without the use of them, the entire understanding of atomic and molecular orbitals would not have advanced to the well developed state that it is in today. Consequently, it is only natural for a scientist to take a keen interest in the concept of modeling since it has had such a profound impact of the field of science.

Furthermore, the field of mathematical modeling in the biosciences has flourished for decades. However, it has only been in the last fifteen years that immunological modeling has come into being [3]. Moreover, the field of mathematical modeling of cancer immunology remains in its infancy. To date, no rigorous models of the human body's immunological response to tumors are known.

Nevertheless, this does not explain what benefits could be achieved from immunological modeling of cancer systems. The benefits are the same as with any other type of modeling, gaining a better understanding of the system involved and helping future research in that area [20]. If one creates a model in which several assumptions are made, whether or not the results of the model correlate to the actual experimental results will help determine if those assumptions were valid. Thus, if the experimental and model results are similar, one can deduce that the theories behind the model are plausible and worthy of further investigation. Conversely, if the experimental and model results are not similar, it can be inferred that the theories used to create the model must somehow be incorrect and new ideas need to be utilized. Therefore, by a trial and error process, concepts and ideas concerning the

mechanisms by which the human body's immune system responds to cancer can be tested for their validity. Eventually, a correct and accurate model of cancer immunology can be arrived at. This new model would be the product of a better understanding of some of the mechanisms of the human body's immune system.

Armed with this better understanding of some of the cancer mechanisms, researchers could investigate possible avenues for treatments based upon the model. In doing so, a simple working model of cancer immunology could save a researcher countless hours of time by directing research towards possible solutions and away from experiments which would yield ineffective results. Moreover, an immune system model could help a researcher discount particular experiments, since those experiments would be most likely to produce uninteresting results. Similarly, such a model could aid a researcher in creating experiments that would produce the most dramatic and, *hopefully*, the most significant results.

Although this type of cancer research, immunological modeling, cannot hope to nor ever boast to cure cancer, it can provide invaluable information about the mechanisms of cancerous growths, and thereby increase our understanding of cancer. This contribution, as small as it may be, will be another piece in the large puzzle which will lead to the eventual cure for cancer.

Introduction to Immunology

An extensive introduction into the topic of immunology is necessary for two reasons. First, immunology is a very specialized topic; its mechanisms and vocabulary are not understood by most. Further, a long introduction into

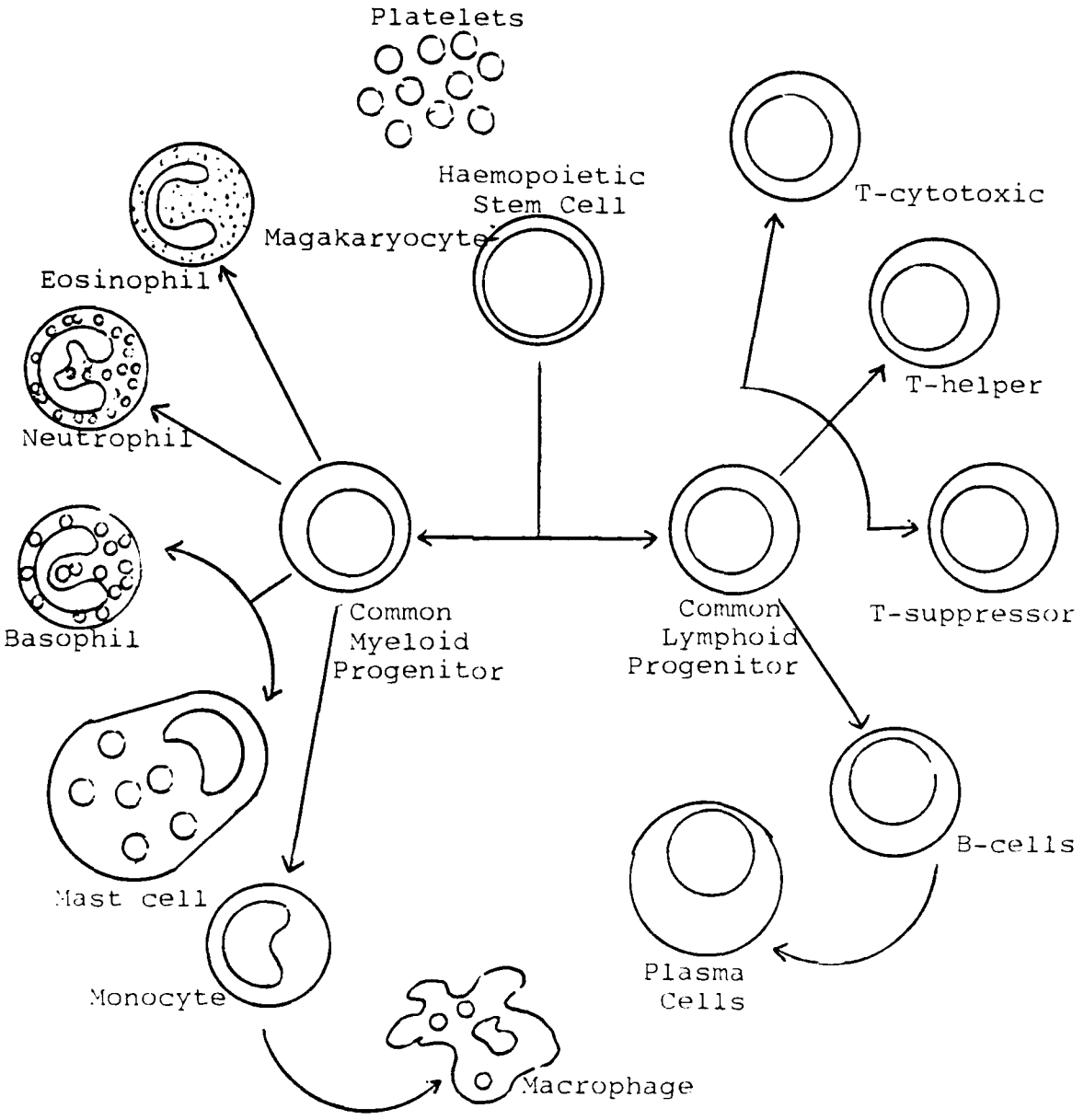
immunology is in order since a large portion of time, some five months total, was spent researching through the literature to gain the best possible understanding of immunology and, in particular, how immunology relates to cancer, since all of the immunology learned for this Trident Project was done subsequent to becoming a Trident Scholar.

The immune system is simply the human body's defense mechanism against any foreign object [21]. Those foreign bodies can be bacteria, viruses, fungi, parasites [19], transplanted organs [14], or cancer cells [28]. The immune system was developed to be able to detect, isolate, attack, and destroy any of these foreign invaders, including cancerous tumors [16]. Any one of these organisms could kill their human host if allowed to propagate unchecked by the immune system. In fact, the vast majority of these infections are limited in duration and leave few lasting residues [5]. This is all a credit to the human body's immune system.

Undoubtedly, the immune system is one of the most complex of organizations within the human body. The body's immune system contains diverse molecules, including antibodies and hormone-like stimulators, many kinds of living cells, and an overall programming that is extremely complex. In spite of this complexity, all of the cells of the immune system come from one common stem (figure 1) [19]. This haemopoietic stem cell serves as the basis for both the cells of the blood stream, as well as the cells of the immune system. From this common origin, the cells first differentiate into the myeloid lineage, responsible for the cells of the blood, and into the lymphoid lineage, responsible for the cells of the lymphatic system. The myeloid lineage further differentiates into the red blood cells, white blood cells, and phagocytes of the blood stream [14]; the lymphoid cells, which are

Figure 1

Origin of Cells involved in the Immune Response



All the cells are derived from pluripotent stem cells. These give rise to two distinct progeny, one of the lymphoid series and the other of the myeloid series. The common lymphoid progenitor has the potential to differentiate into either T- or B-cells depending on the environment to which it 'homes'. The myeloid cells differentiate into the committed cells shown here.

of primary interest in this study, differentiate into the immunologically active cells.

These lymphocytes make up much of the bulk of the immune system. From their common stem, they differentiate into two main categories - the B lymphocytes that synthesize the specialized molecules called antibodies, and the T lymphocytes that work by regulating the immune system and killing invading cells, such as tumor cells. Again, the T lymphocyte cells further differentiate to form three different types of T-cells. The first type is the T-cytotoxic cell which is actually responsible for the cellular destruction mentioned above [8]. Another extremely important type of T-cell is the T-helper cell, which releases hormonal-like stimulating factors which increase the sensitivity of the immune system while simultaneously increasing the proliferation rates of the antibody producing cells of the immune system. Finally, the T-suppressor cell is the counterpart of the T-helper cell, suppressing all of the functions of the immune system in an extremely effective manner [18].

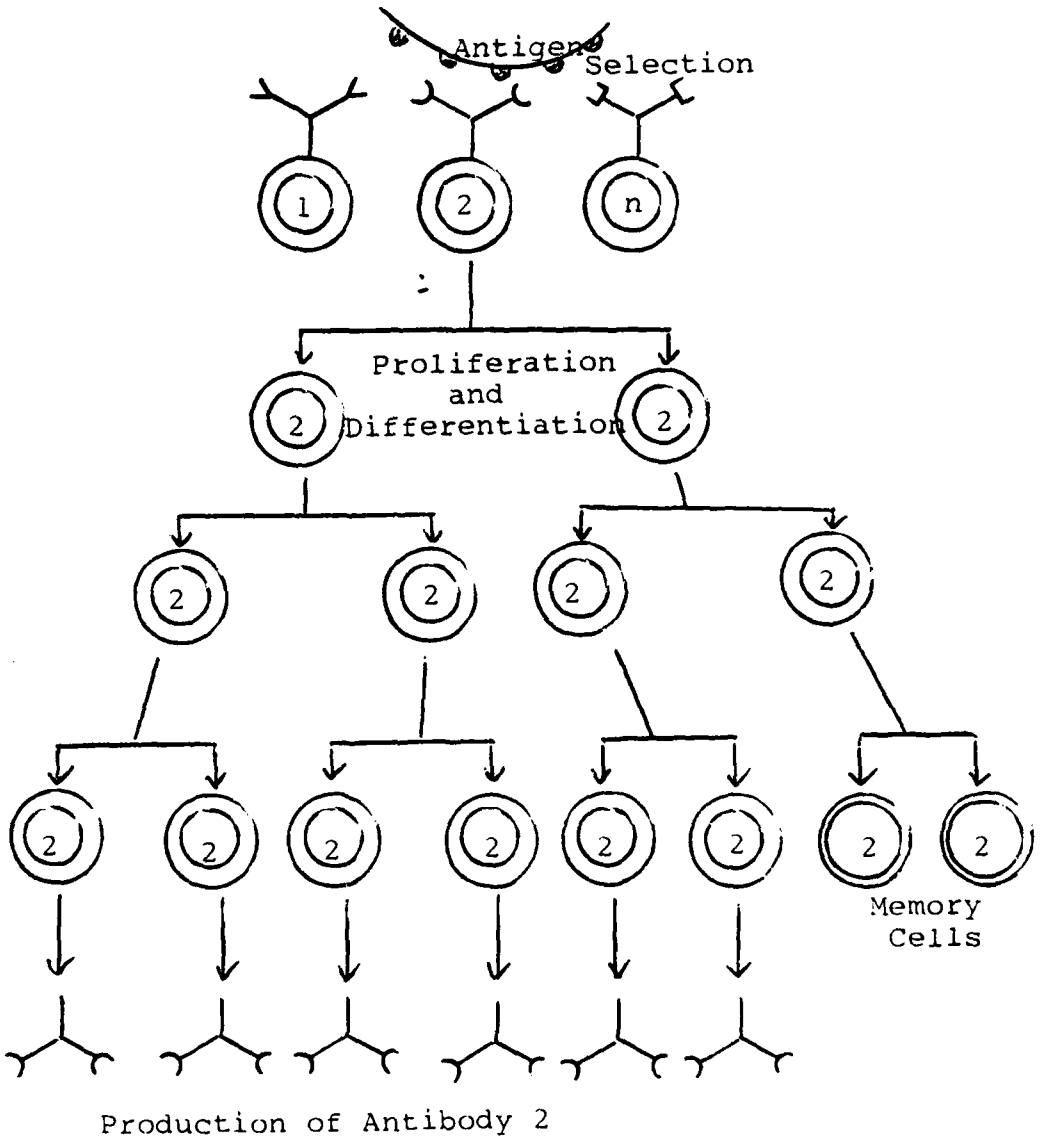
The division between T-cells and B-cells also serves as the division between two separate and distinct ways in which the immune system can react to the infiltration of a foreign organism. The T-cell response is a cellular response in which different types of cells are involved in the destruction of the invading organism. In contrast, the B-cell response is the molecular or antibody response in which antibodies are produced that are specifically designed to attack one type of invader. Both of these responses require the immune system to be able to detect the organism, and differentiate between that organism and the human body's own cells. This is achieved with molecules called antigens [16]. The surfaces of all biological cells are coated

with antigens, including the cells of the human body. Each species, as well as members within a species, possesses cell surfaces which have slightly different molecules or antigens, thus allowing the immune system to distinguish between self and non-self. With all of the cells within a given human body coated with the same antigen molecule, any cell that appears with a different antigen coding will elicit an immune response, and the immune system will begin its attack [15].

One of the ways the immune system can begin its attack is by the stimulation of a B-cell. B-cells are designed to be specific for one particular antigen. Thus, only that particular antigen that the B-cell is coded for can stimulate it [29]. The immune system finds the correct B-cell for a given antigen through a process called clonal selection (figure 2) [19]. Within the human body, there are literally a million million (10^{12}) different B-cells. When the immune system is presented with an antigen, it goes about trying to find the B-cell whose antibody receptors bind the strongest to the antigen presented. In trying to find the B-cell that corresponds to the antigen, a time delay is created in which the foreign organism has the opportunity to grow, expand, and infect other parts of the body. When the immune system finds the B-cell that fits the antigen the best, via a "lock-in-key" type of mechanism, that B-cell is then stimulated by the interactions between its cell membrane and the antigen. The exact intracellular mechanisms by which this stimulation takes place are not well understood [14]. Nevertheless, this stimulation of the B-cell causes the B-cell to proliferate, and in turn, these new B-cells can also be stimulated. Finally, the B-cells differentiate into plasma cells and memory cells [2]. Plasma cells are responsible for the production of antibody. Memory cells, on the other hand, serve the function

Figure 2

Clonal Selection



Each antibody-producing B-cell is programmed to make just one antibody, which is placed on its surface as an antigen receptor. Each B-cell has a different antigen binding specificity (1 to n). Antigen binds to only those B-cells with the appropriate surface receptor. These cells are stimulated to proliferate and mature into antibody-producing cells and long-lived, memory cells, all with the same antigen binding specificity (2).

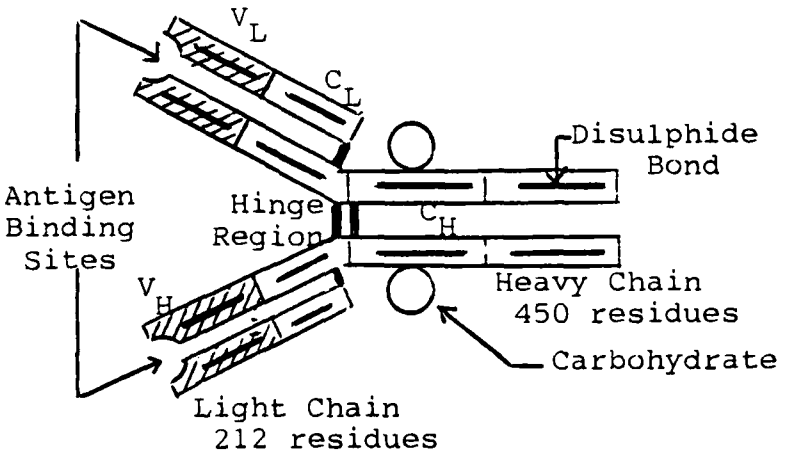
of the memory of the immune system, in case the human body is once again faced with the same antigen [14].

As the plasma cells begin producing antibodies, these specialized molecules (figure 3) [19] begin attaching themselves to the antigens. Just as the B-cells are specific for particular antigens, so too are antibodies. In fact, the structure of a B-cell consists of antibody molecules embedded within its cell membrane. Similar once again to the B-cell, the antibody binds on to the antigen in a "lock-in-key" fashion. A good fit, or binding, between the antigen and the antibody (figure 4) [19] triggers an enzymatic pathway which leads to the eventual destruction of the antigen and the organism carrying the antigen.

In a very similar manner, the T-cell response is initiated. Antigens are presented to the immune system, and subsequently, stimulate a T-cell specific for that particular antigen. This stimulated T-cell then releases chemical products which signal other cells, effector cells (figure 5) [15], to attack. These effector cells can be specific for the antigen, like T-cytotoxic cells, or non-specific, like macrophages [24]. The net result is antigen/organism destruction via cellular interactions, rather than the molecular interactions of the B-cell response.

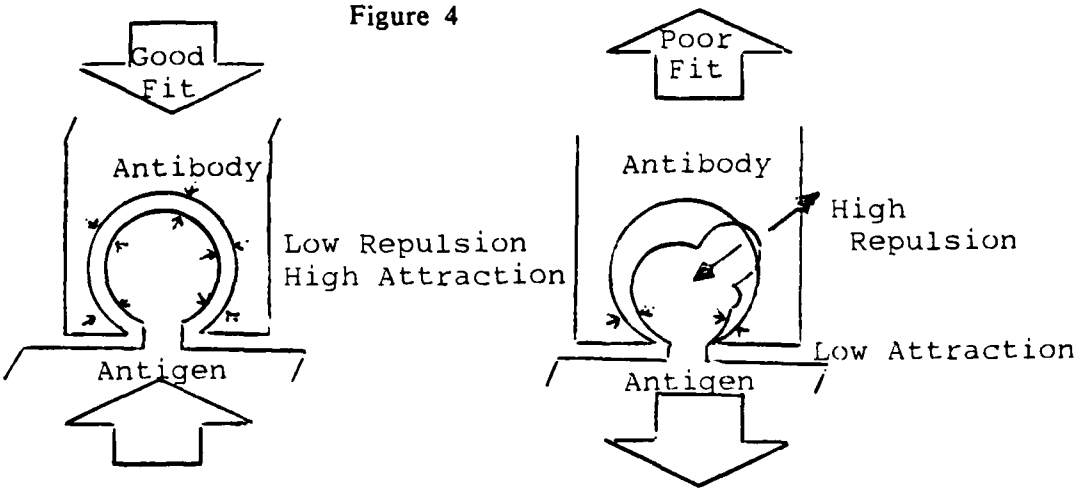
The T-helper and the T-suppressor cells play an extremely important role in both the T-cell and the B-cell responses. The T-helper cell complexes with the antigen of the organism and the appropriate B-cell to form an activated complex (figure 6) [19]. Through a series of interactions between the molecules and cells of the complex, helper factors are released from the T-helper cell. These helper factors can increase the proliferation rate of the immune system, as well as activate other cells. In contrast, the T-suppressor

Figure 3



The basic structure of an Antibody (IgG). The amino terminal end is characterized by sequence variability (V) in both the heavy (H) and light (L) chains. The rest of the molecule has a relatively constant (C) structure. The sites at which the antibody binds to the antigen are located in the variable domains. Further, the flexibility in the hinge region permits variation in the distance between the two antigen binding sites, allowing them to operate independently. Carbohydrate moieties are attached to the C region, which are stabilized by disulphide bonds within the chains.

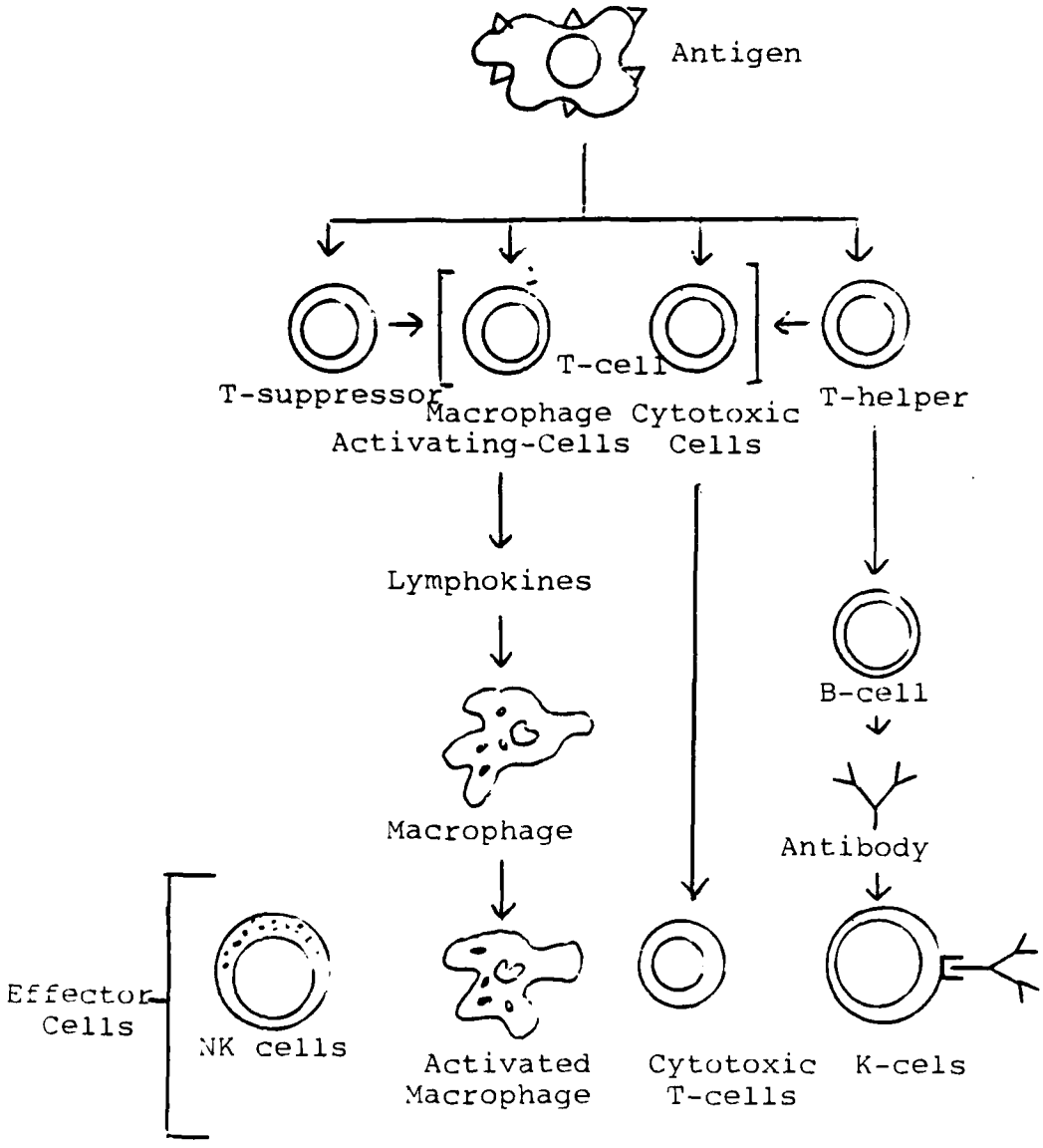
Figure 4



Antibody Affinity. A good fit between the antigenic determinant and the binding site of the antibody will create ample opportunities for intermolecular attractive forces to be created and few opportunities for repulsive forces to operate. Conversely, when there is a poor fit the reverse is true, that is, high repulsive forces are generated when the electron clouds overlap, which dominate any small forces of attraction.

Figure 5

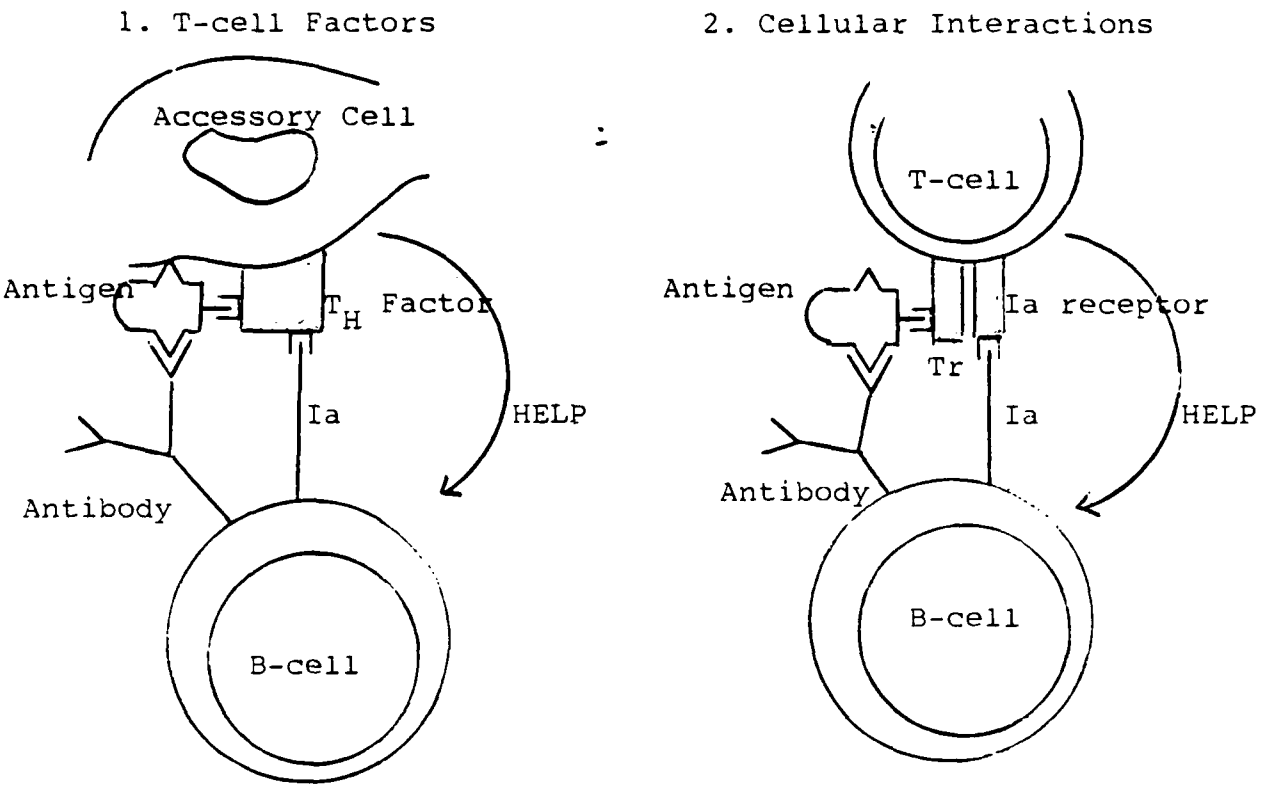
Scope of Cell-mediated Immunity



Cell-mediated or T-cell immune responses follow antigen presentation and activation. Activation is regulated by suppressor and helper cells. Certain T-cells (macrophage activating cells) elaborate lymphokines which activate macrophages to enhance their phagocyte and bactericidal functions. Cytotoxic T-cells are activated by antigen and receive help from T-helper cells. Helper cells also cooperate with B-cells in the production of antibody which may arm cells such as the K-cell for attack. Natural Killer (NK) cells act non-specifically, particularly against cellular targets.

Figure 6

Mechanisms of antigen specific B-cells activation by T-cell help



1. Helper factors specific for the carrier determinants on the antigen (Ag) and on the antibody molecule (Ia) bind to the antigen and deliver a help signal, which, in conjunction with the signal from the B-cell's antigen receptor triggers activation.
2. The T-cell and the B-cell bind antigen via their receptors (TR and Ig) and help is delivered directly to the B-cell. This type of interaction requires cell/cell contact and recognition of the Ia antibody.

cell can suppress all of the immune system's functions. The suppressive factors released by the T-suppressor cells can reduce the proliferation rate of the B-cells, prevent cells from becoming activated, and deactivate already activated cells (figure 7) [14,19]. These two types of T lymphocyte cells can exert a strong, but completely opposite, influence on the human body's immune system.

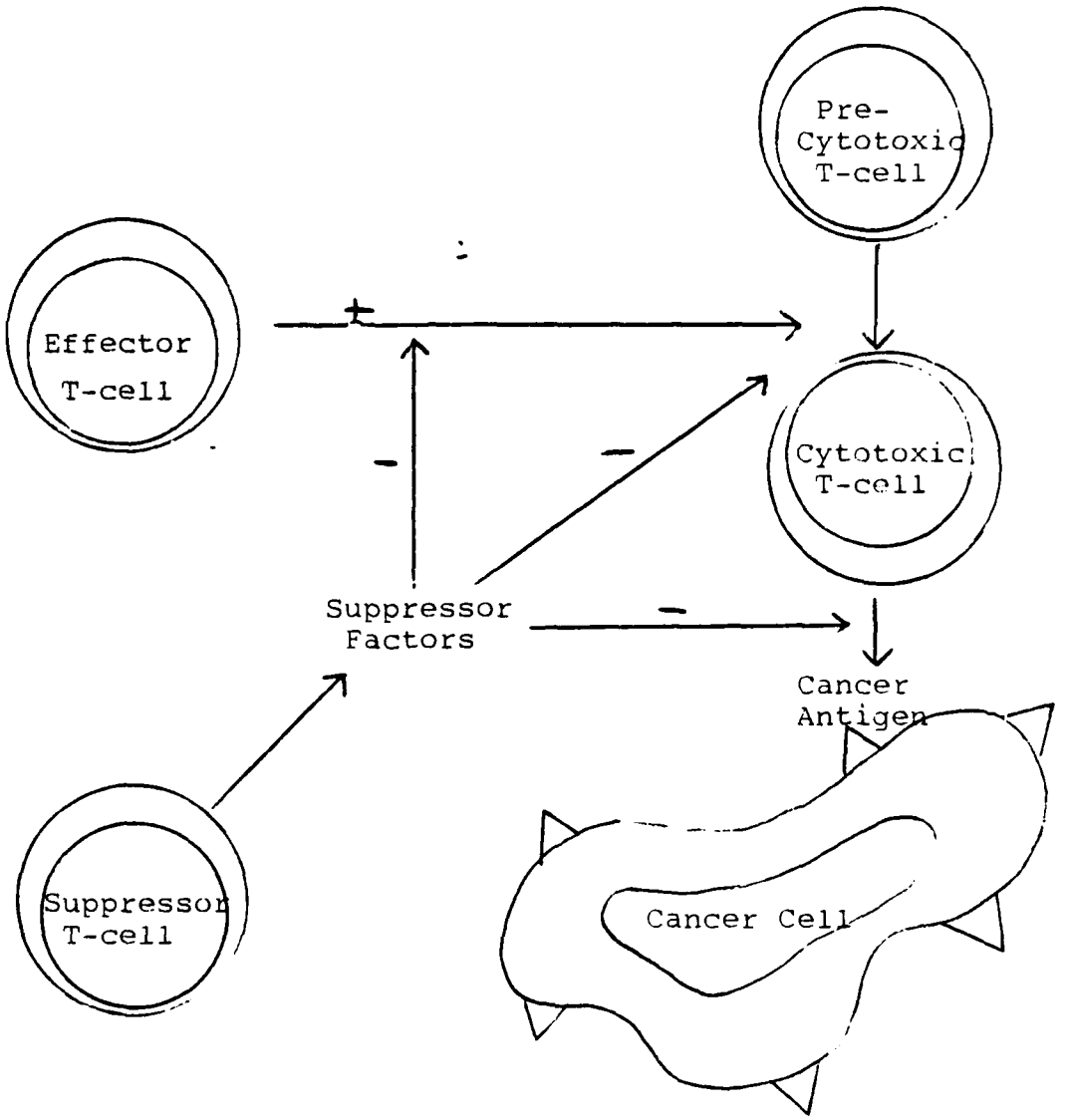
Cancer Immunology

With such an effective means of controlling antigens and the organisms associated with them, it is curious that the immune system sometimes fails to defend against cancer. Cancer cells are simply normal cells that have lost their growth control and have gained the ability to invade new tissues [14]. The transformation of normal cells into cancerous cells by chemical, physical, or viral agents is now beginning to be understood [5,6,19]. Expression of new cell-surface antigens by cancer cells usually allows for them to be recognized and eliminated by the surveillance functions of the immune system. When cancer cells escape this surveillance, life-threatening tumors can result [5].

Normal cellular growth is regulated by two subclasses of cells, proliferating cells and nonproliferating cells. These different types of cells are normally in a ratio such that a steady-state number of tissue cells is maintained. Specifically, in a normal cell system, 99% of the cells are of the nonproliferating variety, while only 1% of the cells are of the proliferating variety [14]. Thus, an even balance between cell death and cell growth is established. In contrast, a tumor tissue does not establish nor maintain this even balance between death and growth. A tumor system can have anywhere from 25 to 100% of its cells of the proliferating type, creating an extremely

Figure 7

T-suppressor cell effects



T-suppressor cells may affect T-cytotoxic cells by having specificity for T-cells, or for the combination of antigen with T-cytotoxic cells, or for antigen alone. Alternately, T-suppressor cells may suppress by direct action on the tumor target cell and thus have receptor specificity for tumor antigens.

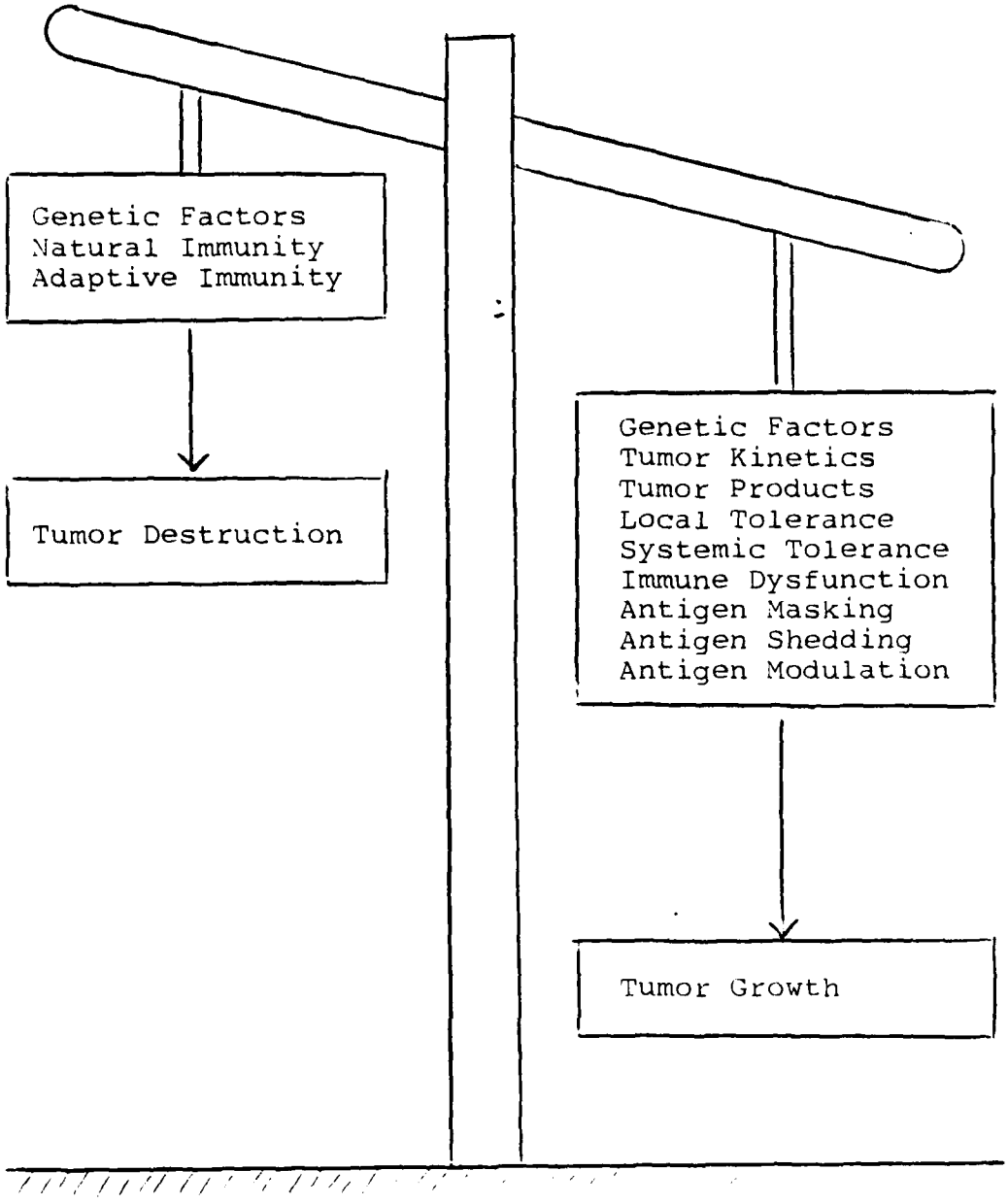
unstable system [12]. The method of tumor formation and of tumor growth can be used to further classify the cancerous growths. A tumor caused by cell proliferation is called a neoplasm (new growth) [14]. Neoplasms that invade surrounding tissues, and eventually spread throughout the entire body via the lymphatic system, are called malignant. On the other hand, neoplasms that do not spread and form isolated tissues are referred to as benign [19]. The origin of the tumor is another means of classification. Neoplasms that develop from epithelial cells (skin and other types of surface cells) are called carcinomas, and those that arise from stromal or mesenchymal cells are called sarcomas [13]. All of these cancer cells can grow and develop within the confines of a normal and healthy immune system. How do these cancer cells escape immune destruction?

The human body itself is a citadel under constant siege. Its billions of cells are subject to frequent outside attack from invaders such as viruses, bacteria, and other microbes [6]. From within, there is also the paramount threat that normal, healthy cells may somehow be converted into uncontrollable cancer cells, trying to push their way into healthy tissues to destroy normal functions. The same capable system that helps to withstand foreign invaders also stands vigilant to prevent and combat cancer. But the rules for fighting cancer are not the same, nor are the parts of the immune system that must wage those battles quite the same [13].

There is a balance of powers between the cancer system and the immune system (figure 8) [19]. In favor of tumor destruction, there are three major factors: genetic factors, natural immunity, and adaptive immunity. Obviously, a family history without any incidence of cancer would lead one to conclude that there are some genetic predispositions to cancer immunity

Figure 8

Immunological Escape



The ability of a tumor to escape from immunological control may depend on a balance between the effectiveness of the immune system and a variety of factors promoting escape.

[13]. Also, the natural immune system plays an important role in the combating of cancer. Unlike the adaptive immune system previously discussed, the natural immune system is a system of non-antigen-specific cells which can destroy a cancerous outgrowth [23]. However, the most significant contribution is made by the adaptive or normal immune system. The adaptive immune system is the system whereby an antigen is presented to the immune system, the immune system finds a means of combating that antigen, and then remembers its attack strategy in case of future antigenic invasion. As mentioned before, the immune system was designed to be able to combat any foreign antigen, including cancer antigens and cancer cells [14]. An important question is how the tumor manages to avoid immune destruction.

There are actually numerous mechanisms and combinations of mechanisms by which cancerous tissues can survive an immune attack, some of which are better understood than others. All of these various mechanisms can be sorted into nine basic categories. The first category involves genetic factors. A genetic predisposition for cancer and cancerous growths can play a major role in any immune attack [13]. Another contribution towards cancerous growth is tumor kinetics. By definition, cancer cells are rapidly dividing and growing cells. Thus, if a cancer system is growing at such a fast rate that the immune system cannot produce cells and molecules fast enough, the neoplasm will be allowed to grow. In addition, the tumor can aid its cause by producing chemicals which inhibit the immune system. A cancer tissue can produce immunosuppressive factors which slow down or completely halt the actions of the immune system. Consequently, these chemical inhibitors can provide the neoplasm an effective defense against destruction [18]. There are also cases in which the immune system simply

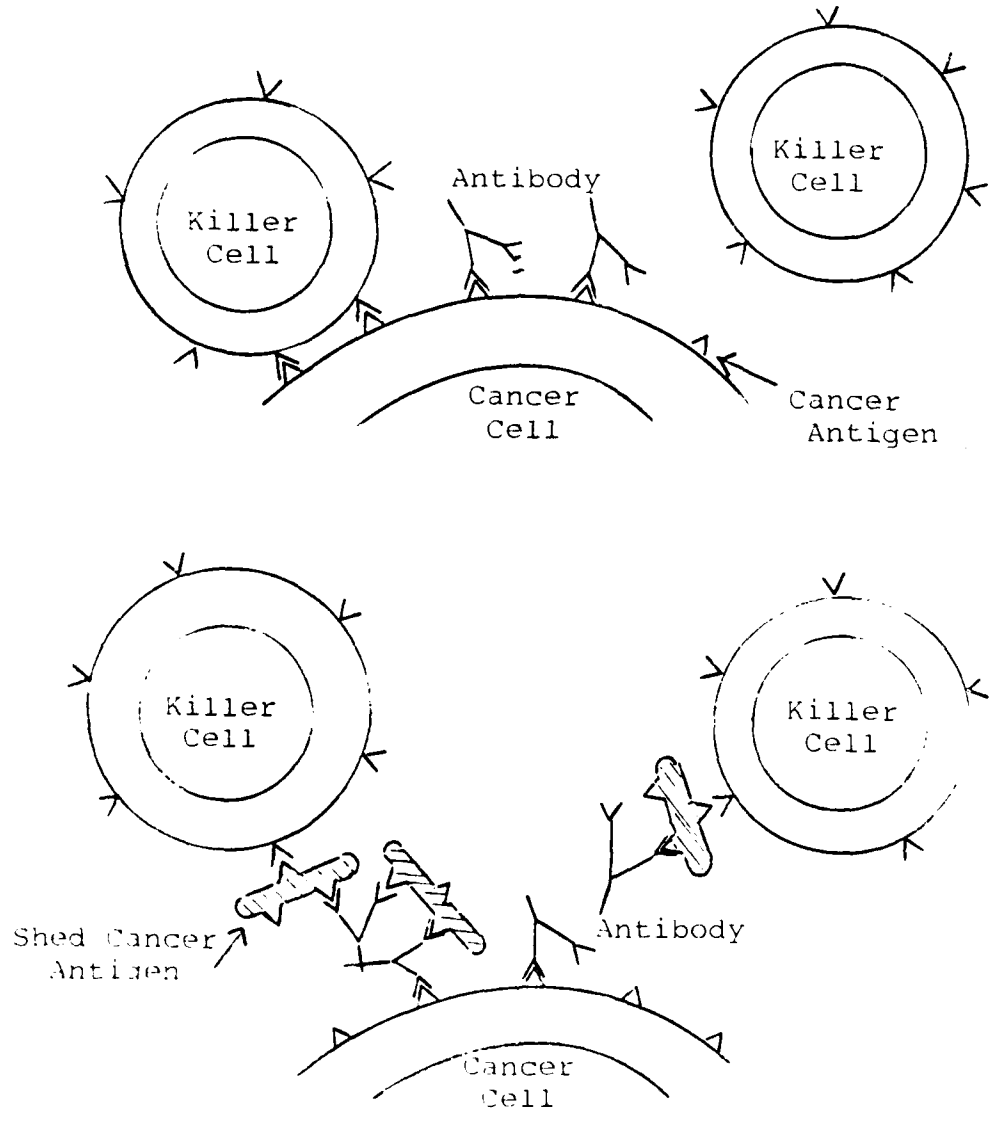
fails to recognize the cancer antigen as foreign, and takes no action against it. If this failure is localized, it is referred to as local functional tolerance; however, if this tolerance to the cancerous antigen is spread throughout the entire body, it is called systemic tolerance. It is not surprising that the immune system might have difficulty differentiating between a cancer cell and a normal, healthy cell, since they share a common origin [12]. Further, the cancer can grow due to the immune system not working. This type of immune dysfunction is traumatic, but highly uncommon [19]. Even patients with total systemic cancer, i.e., cancer throughout their entire body, have been shown to exhibit normal immunological responses when presented with antigens, other than those encoding for cancer [13].

The final three categories of immunological escape are antigen masking, antigen shedding, and antigen modulation. In antigen masking, the cancer cell internalizes its antigens within the surface of the cell membrane. Consequently, when the immunosurveillance system views the cancer tissue, it is not presented with any antigen, and therefore, does not elicit any response [16]. Oppositely, in antigen shedding, the cancer cells shed their antigen molecules off of the surface of their cell membranes. These antigens can then form a wall of defense against incoming immunological attacks (figure 9) [14]. As antibodies of the immune system begin to envelop the cancerous tissue, they are met by and must first destroy a barrier of shed cancer antigen.

The final mechanism of immunological escape is antigen modulation. In this mechanism, the cancer cells modulate or change their antigen code when in the presence of large quantities of bound antibody [4,13,23]. Since it has been shown that a simple change of one hydroxyl group (-OH) in one amino

Figure 9

Blocking Factors



During a normal immunological response, antibodies and natural killer cells are free to interact with the antigens of the cancer cell surface (top), as opposed to the escape mechanism shown (bottom). Antigen (shaded) or antibody-antigen complexes form lattices that may obscure target cell antigenic determinants or killer-cell receptors, or both.

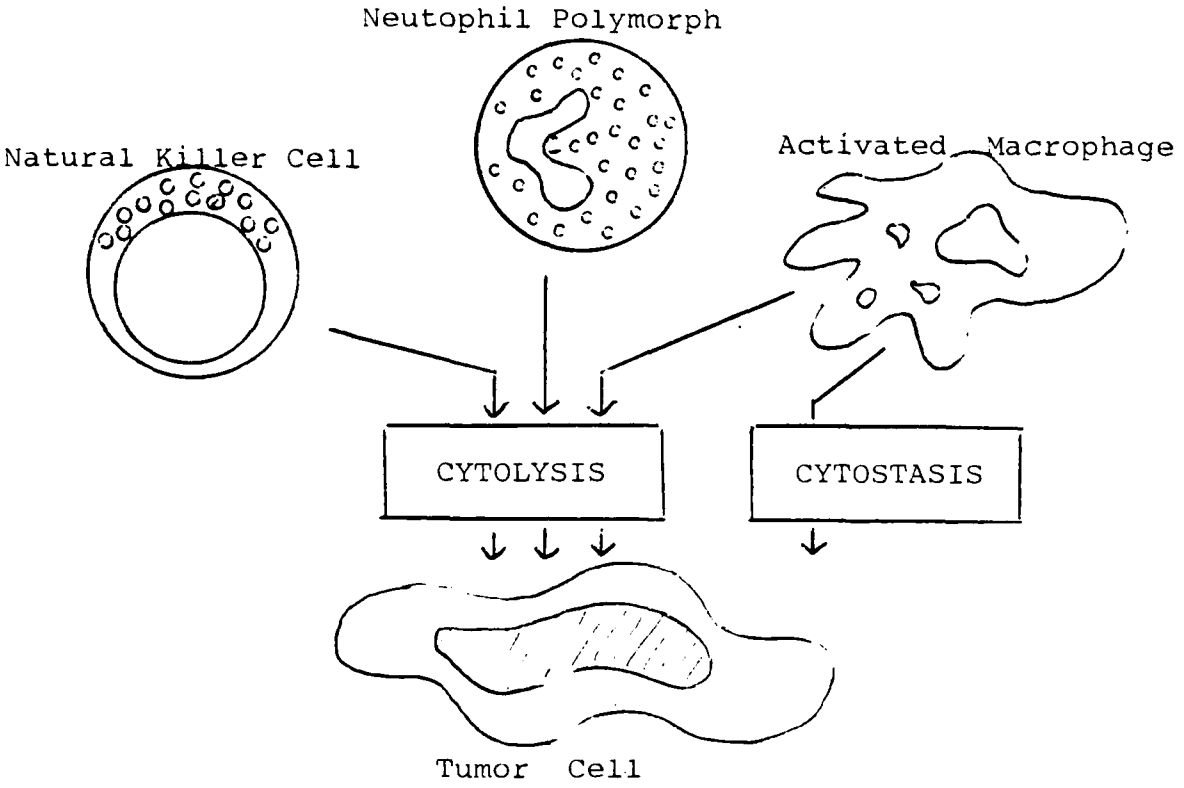
acid unit of the 200+ amino acid residue antigen binding region of an antibody can cause a one thousand fold difference in the anti-body/antigen affinity [3], any change in the antigen surface will have a profound impact on the effectiveness of the immune response. Thus, with a very small change in the antigen molecule, the entire immune response for a specific cancer antigen can be made ineffective. These escape mechanisms are extremely powerful and can humble even the fiercest immunological attacks.

Just as there is the T-cell (cellular) response and the B-cell (antibody) response for viruses, bacteria, fungi, and other foreign organisms, there are T-cell and B-cell immunological attacks of tumors. In the T-cell response, T-cells specific for the cancer antigen are stimulated. These stimulated T-cells release a large number of immunological enhancing factors. Those factors include migration inhibiting factors, macrophage activa-ting factors, chemotactic factors, lymphotoxins, and interferons [18]. All of these lymphokines aid the immune system in directing attacking cells or effector cells to the target cancer, and in containing the cancer tissue. Next, under the chemical guidance of the T-cell lymphokines, the effector cells begin their attack. With the three basic types of effector cells (macrophages, polymorphs, and natural killer cells), the attack can follow two different paths (figure 10) [19]. The first path is cytolysis which causes tumor cell lysis. The second path is cytostasis which inhibits cancer cell growth. Both pathways are effective in regulating the normally unbounded growth of a cancerous tissue [17].

As with any other immune response, there is a B-cell or antibody response. The cancer cell presents its antigens to the immune system and can stimulate the specific T-cell and B-cell corresponding to that antigen (figure

Figure 10

T-cell mediated immunity to Tumors

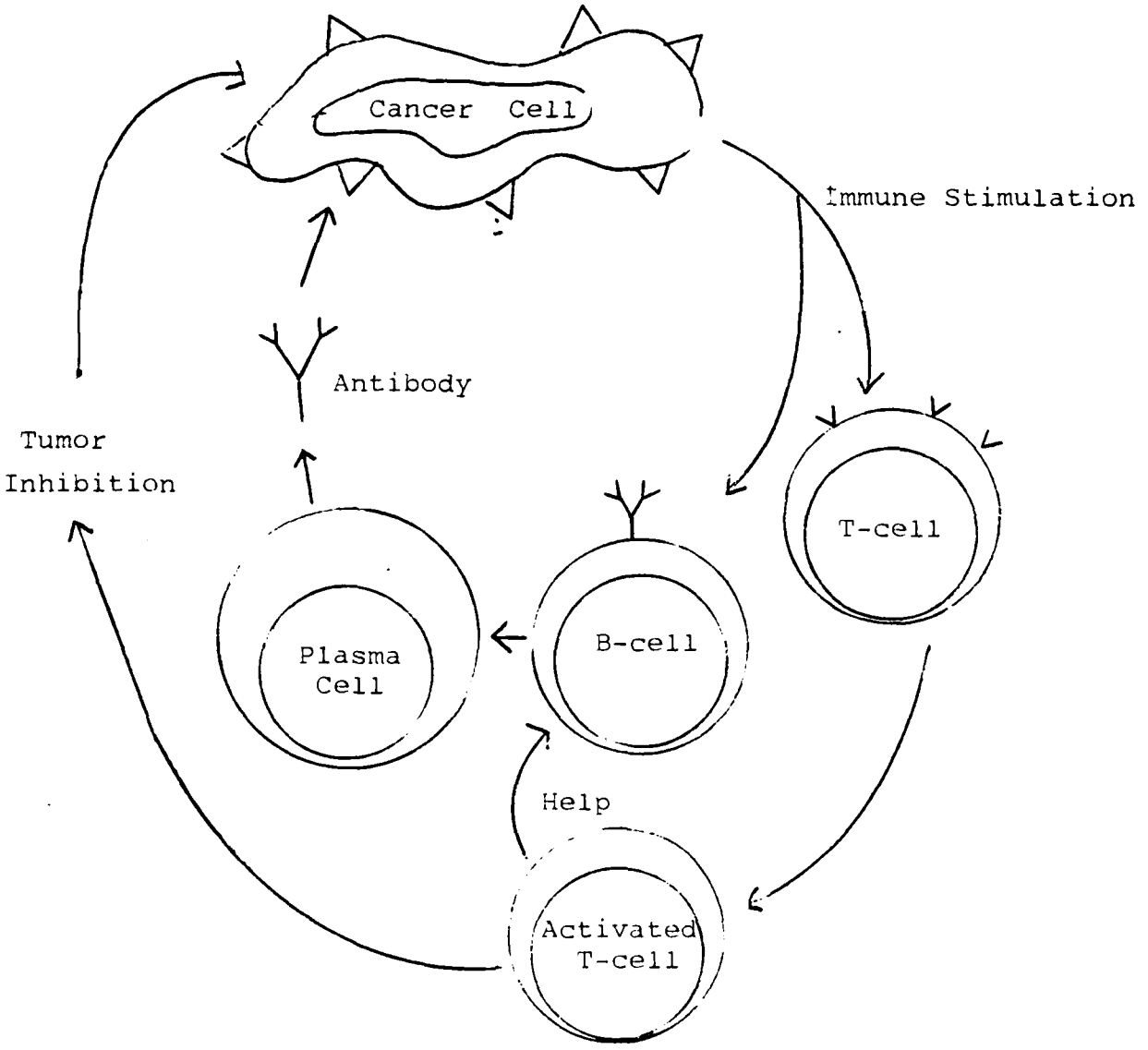


Natural immunity to tumors is mediated by activated macrophages, neutrophils, and natural killer (NK) cells and stimulated by antigenic specific T-cells. Their action may be cytolytic, causing tumor cell lysis, or cytostatic, inhibiting growth. This type of immunity does not require antibody-the cells attack all tumor cells of a particular type.

11) [29]. The stimulated B-cell can then proliferate and differentiate into plasma cells. These plasma cells are then ultimately responsible for the production of antibody and the destruction of the cancer. In addition, the T-cell can become activated and aid the antibody response. The activated T-cell can produce lymphokines which will increase the proliferation rate of the B-cells, as well as decrease the proliferation rate and the migration of the neoplasms. Thus in a manner very similar to that of any normal immune response, the B-cell and T-cell immunological responses work together to destroy the cancer (figure 12) [19].

Figure 11

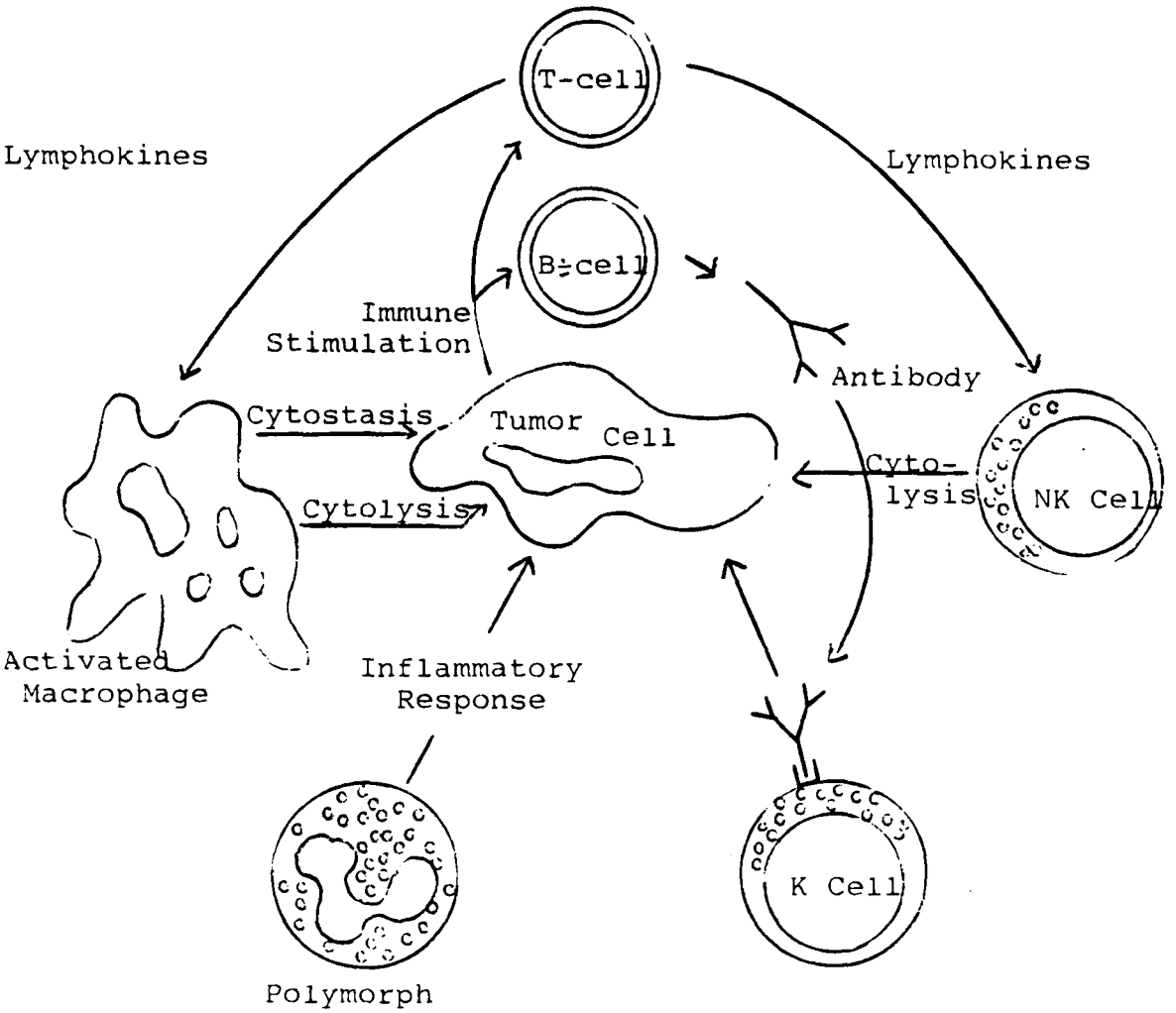
Adaptive immunity to Cancer



Antigens from neoplastic cells bind to antigen-presenting cells and, in association with other antigens, stimulate specific T- and B-cells. The activated lymphocytes cooperate in the production of tumor specific antibodies, as well as the production of cancer inhibiting factors.

Figure 12

Summary of the interactions between the T-cell and B-cell immunological responses



Lymphokines activate macrophages and natural killer (NK) cells. Activated macrophages produce complement components locally which are involved in the development of the inflammatory response. K-cells are armed by antibodies from tumour specific B-cells. This scheme should be interpreted in the awareness that amplifying mechanisms only are shown. Negative interactions have been previously discussed.

Methods

In order to develop a mathematical model for the complex interactions of the human body's immune system, particularly as it relates to cancerous systems, recursion relation equations were used to approximate the results of coupled, ordinary differential equations [22]. This was found to be convenient (though approximate) since it allowed time delays and other discontinuities to be incorporated. These recursion relation equations were of the form:

$$F_{(t+1)} = Q(F_{(t)})$$

where F is a set of variables undergoing dynamical propagation and Q is intricate function which couples the variables. Hereby, the computer could be effectively employed to perform numerous simultaneous, step-wise iterations over a long period of time. Further, with the aid of the computer, the step size of these iterations could be varied so as to obtain better accuracy or better run time.

The actual model which was created was designed to simulate the immune response to a cancerous growth which has demonstrated the ability to modulate its antigens over time. Some actual examples of antigenic modulating cancer systems are leukemias, sarcomas [14], and lymphomas [23]. Thus, a generalized model, applicable to any of the previously mentioned cancer systems, was developed that would not only account for the immunological response, but would also account for a cancer cell which could change its antigen code with time. In order to keep the model's applications as general as possible (since the cancer system/immune system interactions of different tumors vary widely in their ranges and concentrations), a time scale

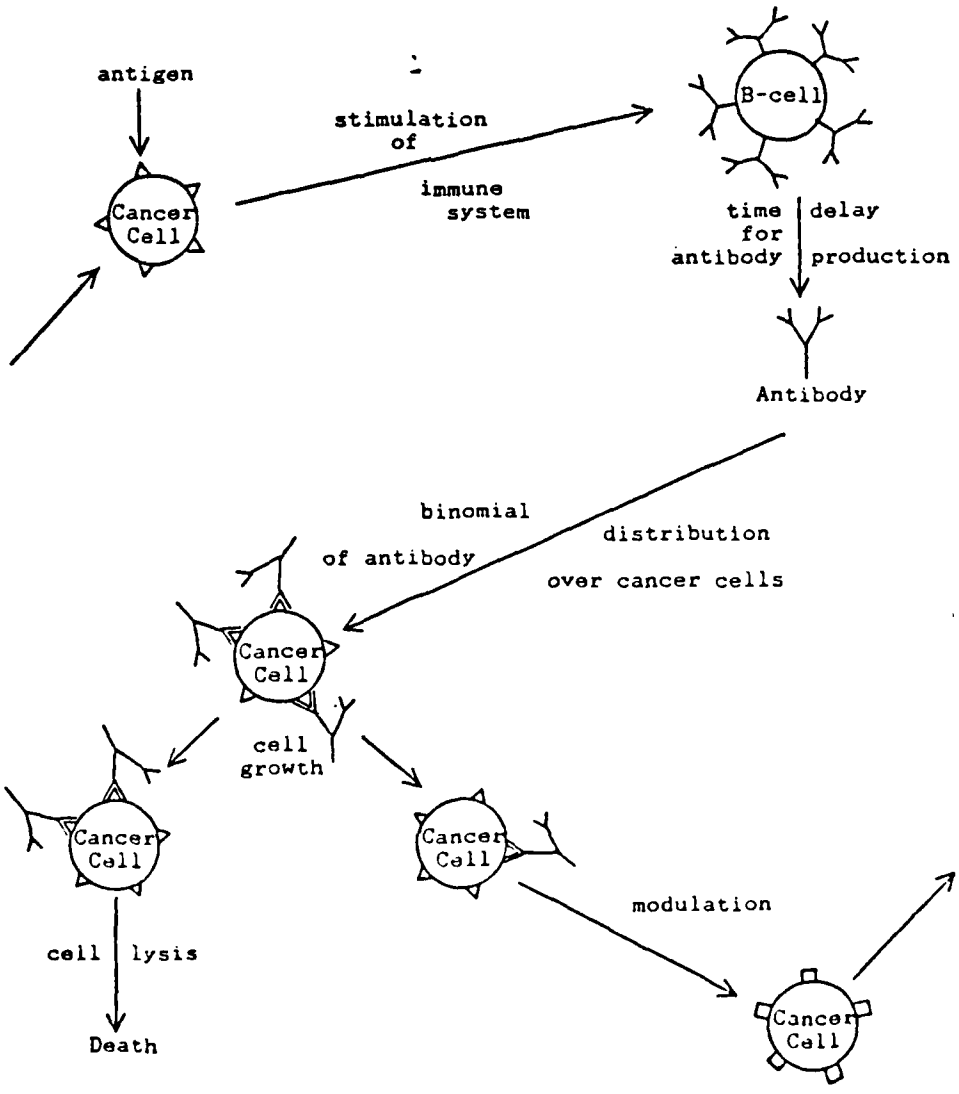
was used which could be applied to any cancer system. For example, one time unit used in this model would roughly correspond to the time of one cell division (15 minutes to one hour) [3]. This allowed each model parameter to be evaluated upon its own merits.

The initial design of the model was based on the growth of one cancerous cell in the first modulation with 25 antigen sites available. Then during each unit of time, the antigens on the cancer cells of each modulation were allowed to stimulate the immune system (figure 13). This stimulation would in turn produce antibodies, after a significant period of time delay. Based on experimental evidence [25,29], a time delay of ten time units was used to simulate the immune system's inherent delay. The amount of stimulation and, consequently, the amount of antibodies produced were proportional to the number of unbound cancerous antigen sites that were presented. Although this is a gross simplification of the intricate mechanisms by which B-cells are stimulated and eventually produce antibodies, it does produce the same characteristic curves that are observed in experimentation [13].

Next, the antibodies of each modulation were allowed to interact with the corresponding cancer cell antigens of their particular modulation. Since antibody/antigen interactions result in almost instantaneous equilibria (when compared to the slower rates of cell division [17]), it was possible to allow the antibodies to completely dissociate from and then redistribute over the antigens of the cancer cells without monitoring the detailed dynamics. Instead, the antibodies were allowed to randomly distribute over the tumor antigen sites by use of a binomial distribution function which is the appropriate distribution function for this type of interaction [21]. The

Figure 13

Modeling of Cancer Immunology



number of cancer cells of each modulation with no antibodies and with from one to twenty-five antibodies attached were placed into separate segments of an array. Then this array was manipulated, one segment at a time, to determine the number of cancer cells that would experience cell lysis due to antibodies being bound to their surface. From experimental results [8,12], it is found that the amount of cell lysis increases nonlinearly with increasing numbers of anti-bodies bound to the surface of the cell. In addition, experiments seem to indicate that there are a minimum number of antibodies required for cell lysis, and that the critical number appears to be two [29]. Moreover, in order to properly account for all antibodies, it was assumed that antibodies on destroyed cancer cells were removed from the system. Thus, these concepts of nonlinear increase and minimum numbers were incorporated into the mathematical model (see figure 15).

Subsequently, the cancer cells were allowed to proliferate. The amount of proliferation per unit time was based upon a portion of the cancer cell population being proliferating-type cells. Per unit time, the proliferating cells were allowed to divide once to produce progeny with the same ratio of proliferating cells to nonproliferating cells as the original cells, and without any antibody attached to them. This method of growth has been proposed by clinical immunoassay studies [27].

Finally, the cancer cells were allowed to modulate or change to the next type of cancer cell. Experimentally, it has been shown that modulation is based upon a great number of factors including temperature and chemical factors, but the greatest influence upon modulation is the number of antibodies bound to the cell surface [21]. Using this concept of numbers of bound antibodies, a model was created in which cells would not modulate

until they had reached saturation or near saturation levels of antibodies, which is the idea proposed by the laboratory results. Using a developed normalizing factor for the average number of antibodies bound to the cancer cell at saturation (figure 14), a ratio of average antibody per cancer cell to the normalizing factor raised to a large exponent was used to determine the number of cancer cells which would change their antigen surface to become cancer cells of the next modulation.

Successively, each modulation was evaluated during each unit of time. By this method, the growth and modulation of the one initial cancer cell could be tracked over time. This tracking could be done both as a function of the number of cancer cells in each specific modulation, or as a function of the sum of the cancer cells in all of the modulations viewed. The equations used for these calculations are outlined in figure 15. In addition, the computer program used to generate the model's results is enclosed in the appendix.

Figure 14

Derivation of Normalizing Factor

Average Antibody(Ab) = Sum of $(n \cdot C[n])$ / Total number of antibodies

where n = the number of antibodies bound to the cancer cell

C[n] = the number of cancer cells with a antibodies bound to it

Normalizing Factor = infinite time limit of the average antibody without modulation

let S = the number of antigen binding sites per cell
D = the proportionality of cell lysis
G = the fraction of proliferating-type cancer cells

At the infinite time limit, antibody concentration will be at a maximum. Consequently, all the antigen sites on the cancer cells will be bound with antigen as the model proceeds to the cell lysis and cell growth steps of its calculations.

Cancer Cell Lysis:

$C[n,t] = C[n,(t-1)] - C[n,(t-1)] \cdot D^{(1/n)}$

$C[S,t] = C[S,(t-1)] - C[S,(t-1)] \cdot D^{(1/S)}$; at saturation

Cancer Cell Growth:

$C[S,t] = C[S,(t-1)]$; at saturation

$C[1,t] = C[S,(t-1)] \cdot G$; at saturation

$C[S,(t-1)]$ = total number of cancer cells at saturation
$= Cs$

$C[S,t] = (1-D^{(1/S)}) \cdot C[S,(t-1)]$
$= (1-D^{(1/S)}) \cdot Cs$

$C[1,t] = G \cdot Cs$

$C_{(tot)} = C[1,t] + C[S,t]$
$= G \cdot Cs + (1-D^{(1/S)}) \cdot Cs$
$= (1+G-D^{(1/S)}) \cdot Cs$

$Ab_{(tot)} = S \cdot C[S,t] = S \cdot (1-D^{(1/S)}) \cdot Cs$

Normalizing Factor $= Ab_{(tot)}/C_{(tot)}$

$= S \cdot (1-D^{(1/S)}) \cdot Cs / (1+G-D^{(1/S)}) \cdot Cs$
$= S \cdot (1-D^{(1/S)}) / (1+G-D^{(1/S)})$

Figure 15

Modeling Equations

Antibody Formation:

$$Ab[m,t] = Ab[m,(t-1)] + Ka \cdot Ag[m,(t-10)]$$

Cancer Cell/Antibody Complex Formation:

$$C[m,n,t] = S!/(n! \cdot (S-n)!) \cdot P^{n} \cdot (1-P)^{(S-n)} \cdot C[m,t]_{(tot)}$$
$$P = Ab[m,t]/(S \cdot C[m,t]_{(tot)})$$

Cancer Cell Lysis:

$$Ab[m,t] = Ab[m,(t-1)] - n \cdot (1-D^{(1/n)}) \cdot C[m,n,t]$$
$$C[m,n,t] = (1-D^{(1/n)}) \cdot C[m,n,(t-1)]$$

Cancer Cell Growth:

$$C[m,1,t] = C[m,1,(t-1)] + G \cdot C[m,t]_{(tot)}$$

Cancer Cell Modulation:

$$C[m,t]_{(tot)} = C[m,(t-1)]_{(tot)} + (\text{avg.}Ab/NF)^{Km} \cdot C[(m-1),t]_{(tot)}$$

where:

$C[m,n,t]$ = the number of cancer cells in modulation n with n antibodies bound to its surface at time t

$C[m,t]_{(tot)}$ = the total number of cancer cells in modulation m at time t

$Ab[m,t]$ = the number of antibodies specific for cancer cells in modulation m at time t

$Ag[m,t]$ = the number of free antigens from cancer cells in modulation m at time t
= the sum of $(S-n) \cdot C[m,n,t]$ for n from zero to S

S = total number of antigen sites per cancer cell

Ka = factor of antibody formation

D= the fraction of cancer cells that experience cell lysis due to antibodies attached

G = fraction of proliferating cancer cells

Km = exponent of cancer cell modulation

Results

Since the objective of any modeling experiment is to approximate the results obtained from the real systems as closely as possible, the kinetics model of cancer immunology, as developed above, was compared to clinical results. From the experimental results disclosed in the literature [4,9,11,23,26], the data shown in figure 16 was obtained [9]. The parameters of the model were then modified so as to obtain results that demonstrated the same behavior as the experimentation. Specifically, the following parameters were used:

G = fraction of proliferating cancer cells = 0.65

D = fraction of cancer cell that experience cell lysis with 2 antibodies attached = 0.07

Km = exponent of cancer cell modulation = 20

Ka = factor of antibody formation = 50

Utilizing these parameters, the resulting plot of the sum of the cancer cells in the first seven modulations shown in figure 17 was produced. Noting the size, shape, and periodicity of the two sets of results, the first being experimental and the second being those generated from the model, it was concluded that the parameters had been adjusted appropriately to simulate "real world" conditions. Further, this representative solution to the model corresponds to only one set of a series of possible solutions to the mathematical model.

Figure 16

Experimental Results

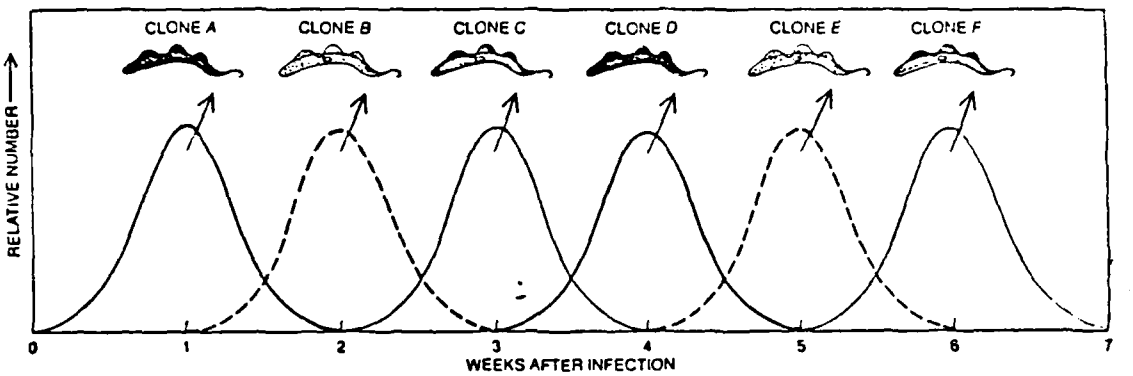
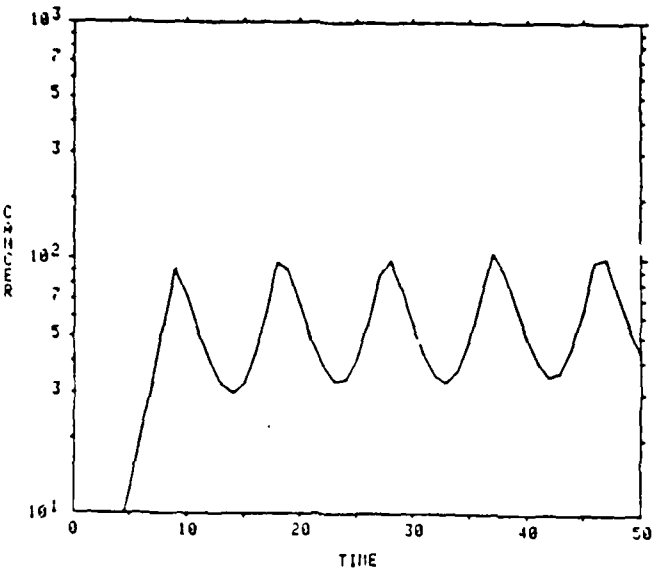


Figure 17

Model Results



Both plots use a base ten logarithm of the relative numbers of cancer cells for the ordinate, and a relative time scale for the abscissa. The top graph is a "smoothed-out" plot of the results obtained from laboratory experimentation. The bottom plot is the results obtained from the mathematical model, shown as a plot of the sum of the cancer cells.

It is worthy to note at this time the axes of the data plots, since they will be used throughout the remainder of the results section. The ordinate of these graphs is a plot of the base ten logarithm of the relative numbers of cancer cells. The abscissa is a plot of relative time in units of time steps or iterations (as defined previously). All of these values have been kept relative, rather than absolute, to ensure the applications of the model are not merely restricted to one cancerous system. If a plot were generated with absolute numbers of cancer cells and an absolute time scale, the results and the model used to generate those results would be specific for that one cancer system. Moreover, this new model would not merely be specific for a type of cancer like leukemia, but rather for an individual cancer disease like moloney thymus-leukemia [23]. Consequently, in the interests of providing a better understanding of general cancer escape mechanisms, the units of the model have been kept as open to general application as possible.

Next, the sensitivity of the various parameters of the model were tested and the results are displayed in the appendix. In addition, the net effects upon the cancer system of these parameter changes is tabulated in table 1. The column on the left shows how the system was altered, with the first entry being the "steady-state" system in figure 17, and the column on the right shows a slope of the oscillating system. This slope was measured based on the peaks of the modulations and expressed in units of decades of relative cancer cells per unit of relative time.

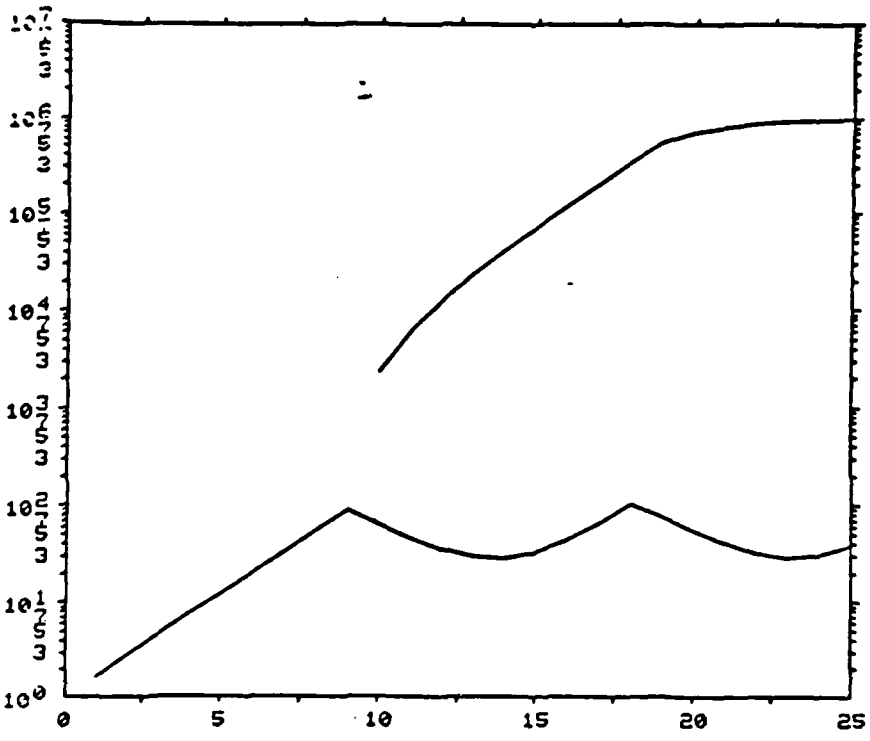
Table 1

System Alterations	Slope (decades/unit of time x 10^3)
"Steady State"	+ 2.1
+100% Antibody Production Rate	+ 1.5
+50% Cell Lysis	- 2.8
-10% Modulation Rate	- 3.9
-10: Growth Rate	- 28.2
-50% Antibody Production Rate	+ 8.6
-90% Antibody Production Rate	+180.

Finally, the immune response, particularly the antibody formation with time, was monitored to ensure that it too correlated to experimental results [21]. The product of this study is shown in figure 18. In particular, it was noted that the maximum number of cells in the second modulation occurred near the maximum level of antibodies for the first modulation.

Figure 18

Immune Response to an Antigenic Modulating Cancer



The ordinate of this plot is a base ten logarithm of the relative number of cancer cells. The abscissa is a plot of relative time. The top curve is a plot of the relative number of antibodies in the first modulation with respect to time. The bottom curve is a plot of the cancer cell sum. Of interest on this plot is the fact that the peak abundance of cancer cells in the second modulation occurs at near maximum levels of antibodies from the first modulation.

Discussion

Discussion of Model Results

The "steady state" model that was created was found to correlate well to the experimental results obtained from the literature [4,9,11,23,26] in size, shape, and periodicity. This correlation between the model and the laboratory results lends credibility to the methods and techniques used to create the mathematical model. Specifically, the concepts of antigen modulation at maximum concentration of bound antibody and of cancer cell lysis being nonlinearly dependent on the numbers of bound antibodies, greater than one, were verified. Although these concepts have been proposed as possible mechanisms involved in the antigenic modulating cancer system by laboratory researcher, the use of this kinetics model of cancer immunology has served to further strengthen the credibility those proposed mechanisms. These concepts could then be used to develop new methods of treatment. For example, if modulation occurs at maximum levels of antibody, then limited immune suppression may be in order. At high levels of antibody, cancer cells modulate, and therefore, avoid immune destruction. Consequently, if the immune system could be controlled so as to produce only low levels of antibody, the cancer cell may not modulate and, assuming a slow enough growth rate, the immune system may be able to destroy the cancer system over time.

Furthermore, other concepts used in the model were strengthened. Those concepts included the use of significant immune system time delays, such as the ten iteration time delay used in this model. When compared to

the cell growth rate of the cancer system, a ten time unit delay was a dramatic lag in the immune system. Although this delay is dramatic and its effects can sometimes be devastating, it cannot be avoided due to the nature of the clonal selection process.

Another concept put forth in the model is the idea of immune stimulation being directly proportional to the number of cancerous antigens. If this remained the only criterion for immune stimulation, the immune system could be stimulated by artificial antigens. These artificial antigens could be created by removing the cytoplasm from normal cancer cells, thus leaving a shell of a cancer cell which only consists of its cell membrane and the antigens attached to it. Thus, these cancer antigens could stimulate an immune response without actually being an immune danger. Moreover, the concept that cancer cell growth depends on a proliferating and nonproliferating cell subpopulations could be utilized also, as this concept was used in creating the model. A researcher could chemically inhibit the rate of cell growth or the fraction of proliferating cells, and thereby give the immune system a chance to combat the antigens of a given cancerous modulation before they grow out of its bounds of control.

Using the information contained within the sensitivity tests of Table 1, the most effective parameters could be varied in a laboratory environment. In the past year, immunological research has made such dramatic strides that such control over immunological parameters as cellular growth and death can be made possible [4]. From Table 1, the most sensitive parameter for cancer cell destruction is the fraction of proliferating cancer cells. Thus, an experiment designed to decrease the cancer cell growth rate would yield the most promising results. On the other hand, based on the sensitivity tests, an

experiment designed to increase the amount of antibody produced would yield rather uninteresting results. However, a noteworthy result was obtained from an increase in the antibody production rate; the resul-ting small change in the growth of the overall cancer system can be attributed to a saturation effect in the antibody concentration over the cancer cells. Regardless, with the aid of this model, experiments could be designed to test some of the most dramatic results, while avoiding such experiments that are believed to be less effective or ineffective.

Future Modeling Research

One of the most serious limitations of this model is the oversimplification used in modeling the stimulation of the immune system. In particular, the model's use of immune stimulation being directly proportional to cancer cell antigen does not allow for lymphokine/cancer cell interactions nor does it acccunt in detailed fashion for T-helper and T-suppressor effects. Thus, the next stage of this kinetics modeling experiment is to incorporate a more rigorous model of the immune stimulation mechanism to include lymphokines, T-helper, and T-suppressor populations.

In this modification to the existing model, cancerous antigen would interact with the immune system on four different levels. The first would be the already accounted for B-cell stimulation to form activated B-cells. These activated B-cells would then be allowed to grow and a certain fraction could differentiate into memory cells and plasma cells. These new plasma cells could, in turn, produce antibodies for tumor attack and another fraction would be allowed to die off.

The second level of antigen stimulation would be the stimulation of

T-helper cells. The antigens of the cancer system would be allowed to interact with the T-helper lymphocytes to form an activated complex. This activated complex would then be able to produce helper factors, which would increase the rate of B-cell activation.

The next level would be the activation of the T-suppressor cells. While antigens are present, they would form complexes with the T-suppressor cells. Via an equilibrium processes, T-suppressor/antigen complexes could separate to form antigens and activated T-suppressor cells, which would produce suppressor factors which would increase the deactivation rate of both the activated B-cells and the activated T-cells. This equilibrium between the complex and the activated T-suppressor cell would be shifted strongly towards the complex; however, in the presence of low levels of antigen, such as those experienced after a successful immune response, a certain finite quantity of activated T-suppressor cells would be created [25].

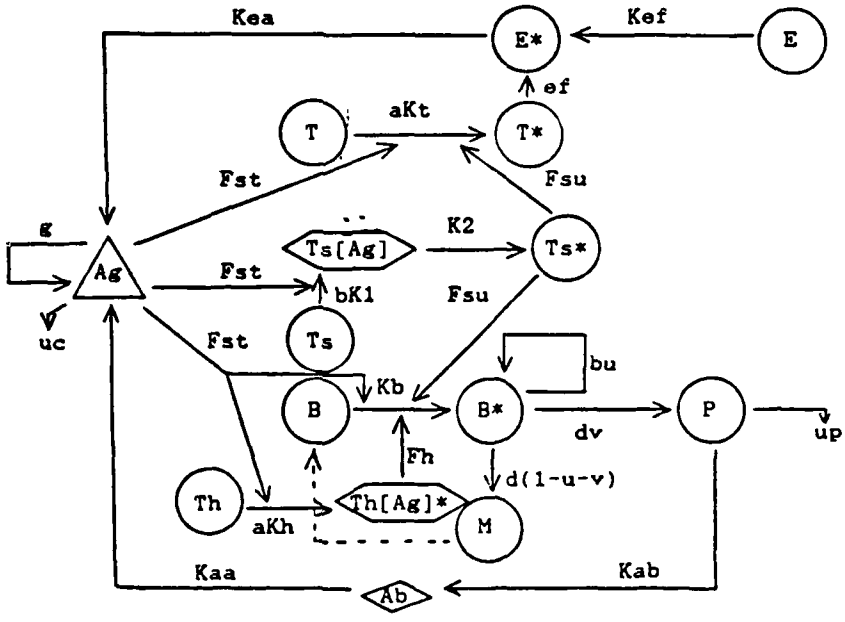
Finally, the fourth level of stimulation would be the T-cell stimulation. Antigens could stimulate T-cells to form activated T-cells. These activated T-cells would then produce lymphokines, such as interferons, which would activate effector cells. These newly activated effector cells could then attack the cancerous antigens and the cancer cells themselves [20].

This more rigorous model could more accurately account for the mechanism by which the immune system is stimulated. Just as the van der Waal's expansion onto the ideal gas law yields more credible results, this new expansion onto the existing mathematical framework of the model will be used to acquire better results, and therefore a better understanding. Further, the new model would allow the effects of chemical factors such as helper factors, suppressor factors, and other lymphokines to be investigated. The method of

this modeling for this new kinetics model is outlined in figure 19. In addition, the equations used to create this model are shown in figure 20. Since the kinetics model of cancer immunology submitted as the finished product in this research project is actually the fifth revision to the original model that was created, it is not surprising that there are no results from this latest model. However, results and conclusions based upon this more rigorous model are anticipated within the next couple months.

Figure 19

New Model of Cancer Immunology



where:

* = activated complex or cell
E = number of Effector cells (macrophages, NK, T-c)
T = number of T-cells
Ts = number of T-suppressor cells
Ts[Ag] = number of T-suppressor/cancer antigen complexes
Ag = number of Cancerous Antigen
B = number of B-cells
P = number of Plasma cells
Th = number of T-helper cells
Th[Ag]* = number of T-helper/cancer antigen activated complexes
M = number of memory cells
Ab = number of antibodies

Figure 20

New Modeling Equations

$$d(Ab)/dt = Kab \cdot P - Kaa(t) \cdot Ab$$
$$d(P)/dt = dv \cdot (B^*) - up \cdot P$$
$$d(B^*)/dt = (bu - dv - d(1-u-v)) \cdot (B^*) + Kb(t) \cdot B$$
$$d(B)/dt = -Kb(t) \cdot B$$
$$d(T)/dt = -aKt(t) \cdot T$$
$$d(T^*)/dt = aKt(t) \cdot T$$
$$d(Ts)/dt = -bK1(t) \cdot Ts$$
$$d(Ts[Ag])/dt = bK1(t) \cdot Ts - K2(t) \cdot (Ts[Ag])$$
$$d(E)/dt = -Kef(t) \cdot E$$
$$d(E^*)/dt = Kef(t) \cdot E - Kea(t) \cdot (E^*)$$
$$d(Th)/dt = -aKh \cdot Th$$
$$d(Th[Ag]^*)/dt = aKh(t) \cdot Th$$

using:

$$Kb(t) = Fst \cdot Ag + Fh \cdot (Th[Ag]^*) - Fsu \cdot (Ts^*)$$
$$Kt(t) = Fst \cdot Ag - Fsu \cdot (Ts^*)$$
$$Kh(t) = Fst \cdot Ag$$
$$K1(t) = Fst \cdot Ag$$
$$K2(t) = (Ts^*) \cdot Ag / (Ts[Ag])$$
$$Kef(t) = ef \cdot (T^*)$$

where:

- u = portion of activated B-cells that are growing
- b = growth rate of B-cells
- v = portion of activated B-cells that are differentiating into plasma cells
- d = differentiation rate of B-cells
- up = plasma cell death rate
- uc = cancer cell death rate
- (1-u-v) = portion of activated B-cells which are differentiating into memory cells
- Kab = plasma cell antibody production rate
- ef = effector factors (lymphokines)
- Kef = activation rate of effector cells
- Fst = factor of stimulation from cancer cell antigens
- Fsu = factor of suppression or suppressor factors
- Fh = factor of help
- Kt = T-cell activation rate
- Kb = B-cell activation rate

Conclusion

The goal of this Trident research project was to create a kinetics model of cancer immunology which correlated to the experimental results found in the literature. In fact, a good, working, and accurate model has been created. As a result of this model, the dependence of antigenic modulation on the number of antibodies bound to a cancer cell has been established. In addition, the nonlinear relationship between numbers of bound antibodies and the amount of cell lysis has been confirmed. Along with this confirmation was the usage of a minimum requirement of antibodies for cell lysis. This is above and beyond the reaffirmation of experimental proposals concerning cellular growth and immune system stimulation.

As a direct result of this model, the mechanism of antigenic modulation, by which some cancers escape destruction by the human body's immune system, is better understood. Consequently, as a result of this understanding, meaningful laboratory experiments can be created by altering some of the most sensitive parameters discovered by the model. The experiments devised as a product of this kinetics model, as well as the man hours saved by avoiding ineffective experimentation, can be invaluable to the cancer research community. In particular, this model can have a direct application to research of systems that display antigen modulating behavior, such as leukemias, sarcomas [13], and lymphomas [3], as well as measles, herpes simplex [21], and, most recently proposed, Acquired Immuno-Deficiency Syndrome [9].

References

1 G. M. Barrow, Physical Chemistry, McGraw-Hill, New York, 1979.

2 G. I. Bell, M. Dembo, and P. Bongrad, Cell Adhesion: Competition Between Nonspecific Repulsion and Specific Bonding, Biophysics Journal, 45:1051-1064 (1984).

3 G. I. Bell, Mathematical Model of Clonal Selection and Antibody Production, Journal of Theoretical Biology, 29:191-232 (1970).

4 V. Bertness, I. Kirsch, G. Hollis, B. Johnson, and P. A. Bunn, T-cell Receptor Gene Rearrangements as Clinical Markers of Human T-cell Lymphomas, The New England Journal of Medicine, 313:534-38 (1985).

5 Cancer Facts and Figures, American Cancer Society, New York, 1985.

6 *Decade of Discovery: Advances in Cancer Research 1971-1981*, National Institutes of Health, U.S. Department of Health and Human Services, Bethesda, 1981.

7 J. F. Desforges, T-cell Receptors, The New England Journal of Medicine, 313:576-77 (1985)

8 W. G. Dippold, A. Knuth, and K. H. Meyer Zum Büschenfelde, Melanoma Antibodies: Specificity and Interaction with Melanoma and Cytotoxic T-Cells, Models and Methods in the Immunotherapy and Chemotherapy of Cancer, Behring Institute Mitteilungen, 74:14-18 (1984).

9 J. E. Donelson and M. J. Turner, How the Trypanosome Changes Its Coat, Scientific American, 242:45-51 (1985).

10 M. Essex, M. F. McLane, T. H. Lee, and etal., Antibodies to Cell

Membrane antigens associated with Human T-cell Leukemia virus in patients with AIDS, Science, 220:859-62 (1983).

11 D. M. Freymann, P. Metcalf, M. Turner, and D. C. Wiley, 6 Angstrom-Resolution X-ray structure of a variable surface glycoprotein, Nature, 311:167-69 (1984).

12 D. Glaves and L. Weiss, Cellular Interactions in Metastasis, The Handbook of Cancer Immunology, Garland, New York, 1981, 6:3.

13 E. Hawrylko, Mechanisms by which Tumors Escape Immune Destruction, The Handbook of Cancer Immunology, Garland, New York, 1981, 2:1-53.

14 L. E. Hood, I. L. Weissman, W. B. Wood, and J. H. Wilson, Immunology, Second Edition, Benjamin/Cummings, Menlo Park, 1984.

15 S. Kontiainen, Functional Stimulation of T-cells with Protein Antigens, The Handbook of Cancer Immunology, Garland, New York, 1981, 6:183-213.

16 G. Möller and E. Möller, Immunological Surveillance against Neoplasia, Immunological Aspects of Cancer, MTP Press, England, 1978, pp. 205-17.

17 A. S. Perelson and C. A. Macken, Kinetics of Cell-Mediated Cytotoxicity: Stochastic and Deterministic Multistage Models, Mathematical Biosciences, 70:161-94 (1984).

18 M. R. Price and R. A. Robins, Circulating factors modifying cell-mediated immunity in experimental neoplasia, Immunological Aspects of Cancer, MTP Press, England, 1978, pp.155-81.

19 I. M. Roitt, J. Brostoff, and D. K. Male, Immunology, Mosby, St.Louis, 1985.

20 N. R. Rose, Autoimmune Diseases, Scientific American, 224:80-103 (1981).

21 L. E. Segel, Mathematical Immunology, Modeling dynamic phenomena in molecular and cellular biology, Cambridge, London, 1984.

22 L. E. Segel, Recursion relations in ecological and cellular population dynamics, Modeling dynamic phenomena in molecular and cellular biology, Cambridge, London, 1984.

23 C. W. Stackpole and J. B. Jacobson, Antigenic Modulation, The Handbook of Cancer Immunology, Garland, New York, 1981, 2:55-159.

24 G. Sundharadas, H. T. Cheung, and W. D. Cantarow, Anti-inflammatory effects of Cancer: A Macrophage-modulating factor produced by Cancer Cells, The Handbook of Cancer Immunology, Garland, New York, 1981, 2:241-58.

25 B. A. Waite and R. N. Hyer, On the Role of Persistent Signaling and Autocatalysis in the T-cell Independent Immune Response, Mathematical Biosciences, 78:193-202 (1986).

26 L. M. Weiss, E. Hu, G. S. Wood, and etal., Clonal Rearrangements of T-cell Receptor Genes in Mycosis Fungoides and Dermatopathic Lymphadenopathy, The New England Journal of Medicine, 313:539-543 (1985).

27 J. M. Williams, B. J. Ransil, H. M. Shapiro, and T. B. Strom, Accessory Cell requirement for Activation Antigen expression and Cell Cycle progression by human T lymphocytes, Journal of Immunology, 133:2986-95 (1984).

28 S. Zolla-Pazner, S. Fleit, and J. P. Kolb, Regulation of the Immune Response by Tumors, The Handbook of Cancer Immunology, Garland,

New York, 1981, 2:225-239.

29 R. H. Zubler and A. L. Glasebrook, Requirement for three signals in "T-independent" (Lipopolysaccharide-induced) as well as in T-dependent B-cell responses, Journal of Experimental Medicine, 155:666-680 (1982).

Appendices

Computer Program

```
1000 OPEN#1:NAME"ANTMOD1"
1010 OPEN#2:NAME"ANTMOD2"
1020 OPEN#3:NAME"ANTMOD3"
1030 OPEN#4:NAME"ANTMOD4"
1040 OPEN#5:NAME"ANTMOD5"
1050 OPEN#6:NAME"ANTMOD6"
1060 OPEN#7:NAME"ANTMOD7"
1070 OPEN#8:NAME"ANTSUM"
1075 OPEN#9:NAME"ANTBOD"
1080 ERASE#1
1090 ERASE#2
1100 ERASE#3
1110 ERASE#4
1120 ERASE#5
1130 ERASE#6
1140 ERASE#7
1150 ERASE#8
1155 ERASE#9
1160 PRINT " ","CANCER CELL MODULATIONS"
1170 PRINT "TIME","MOD 1","MOD 2","MOD 3","MOD 4"
1180 PRINT " ","MOD 5","MOD 6","MOD 7","SUM"
1190 PRINT " ","ANTIBODY IN MOD 1"
```

```
1200 PRINT 0,1,0,0,0 1210 PRINT " ",0,0,0,1
1220 PRINT " ",0
1230 LET S=25
1240 REM S=# OF BINDING SITES PER CANCER CELL VIEWED
1250 LET ST=S
1260 REM ST=TOTAL # OF BINDING SITES PER CANCER CELL
1270 DIM C(7,38)
1280 LET G=0.65
1290 REM G=% OF GROWING CELLS
1300 LET D=0.07 1310 REM D=% OF CELL LYSIS
1320 LET C(1,1)=1
1330 LET C(1,S+2)=C(1,1) 1340 LET C(1,S+3)=ST*C(1,1)
1350 REM THIS INITIALIZES THE CANCER CELL/ANTIGEN CON-
     CENTRATIONS
1360 LET KM=20
1370 REM KM=EXPONENT OF MODULATION
1380 LET KA=50
1390 REM KA=PORPORTIONALITY OF ANTIBODY FORMATION
1400 LET NF=ST*(1-D^(1/(ST-1)))/(1+G-D^(1/(ST-1)))
1410 REM NF=NORMALIZING FACTOR
1420 FOR T=1 TO 200
1430 REM T=SUBJECTIVE TIME
1440 LET SUM=0
1450 REM SUM=THE SUM OF ALL THE CANCER CELLS
1460 FOR M=1 TO 7
1470 REM M=THE DIFFERENT MODULATIONS
```

```
1480 REM **ANTIBODY FORMATION WITH TIME DELAY**
1490 LET C(M,S+4)=C(M,S+4)+C(M,S+5)
1500 LET C(M,S+5)=C(M,S+6)
1510 LET C(M,S+6)=C(M,S+7)
1520 LET C(M,S+7)=C(M,S+8)
1530 LET C(M,S+8)=C(M,S+9)
1540 LET C(M,S+9)=C(M,S+10)
1550 LET C(M,S+10)=C(M,S+11)
1560 LET C(M,S+11)=C(M,S+12)
1570 LET C(M,S+12)=C(M,S+13)
1580 LET C(M,S+13)=KA*C(M,S+3)
1590 FOR N=1 TO (S+1)
1600 REM **CELL/ANTIBODY COMPLEX FORMATION**
1610 LET N=N-1
1620 IF N=0 THEN LET Q=1
1630 IF N>0 THEN GOSUB 2200
1640 LET N=N+1 1650 REM Q=ST!/(N!*(ST-N)!)
1660 IF C(M,S+2)=0 THEN LET P=1
1670 IF C(M,S+2)>0 THEN LET P=C(M,S+4)/(ST*C(M,S+2))
1680 IF P>1 THEN LET P=1
1690 WHEN EXCEPTION IN
1700 LET C(M,N)=Q*P^(N-1)*(1-P)^(ST-N+1)*C(M,S+2)
1710 USE
1720 LET C(M,N)=0
1730 END WHEN
1740 NEXT N
```

```
1750 FOR N=3 TO (S+1)
1760 REM **CELL LYSIS**
1770 LET C(M,S+4)=C(M,S+4)-(N-1)*(1-D^(1/(N-2)))*C(M,N)
1780 IF C(M,N)<1.E-35 THEN LET C(M,N)=0
1790 LET C(M,N)=(1-D^(1/(N-2)))*C(M,N)
1800 NEXT N
1810 REM **CELL GROWTH**
1820 WHEN EXCEPTION IN
1830 LET C(M,1)=C(M,1)+G*C(M,S+2)
1840 USE
1850 LET C(M,1)=C(M,1)
1860 END WHEN
1870 LET C(M,S+2)=0
1880 LET C(M,S+3)=0
1890 FOR N=1 TO (S+1)
1900 LET C(M,S+2)=C(M,N)+C(M,S+2)
1910 LET C(M,S+3)=(S-N+1)*C(M,N)+C(M,S+3)
1920 NEXT N
1930 LET SUM=SUM+C(M,S+2)
1940 IF C(M,S+2)>1 THEN PRINT#M:T;",";C(M,S+2)
1945 IF M=1 THEN GOSUB 2310
1950 REM **CELL MODULATION**
1960 IF C(M,S+2)=0 THEN GOTO 2110
1970 LET P=0 1980 FOR N=1 TO (S+1)
1990 LET P=P+(N-1)*C(M,N)
2000 NEXT N
```

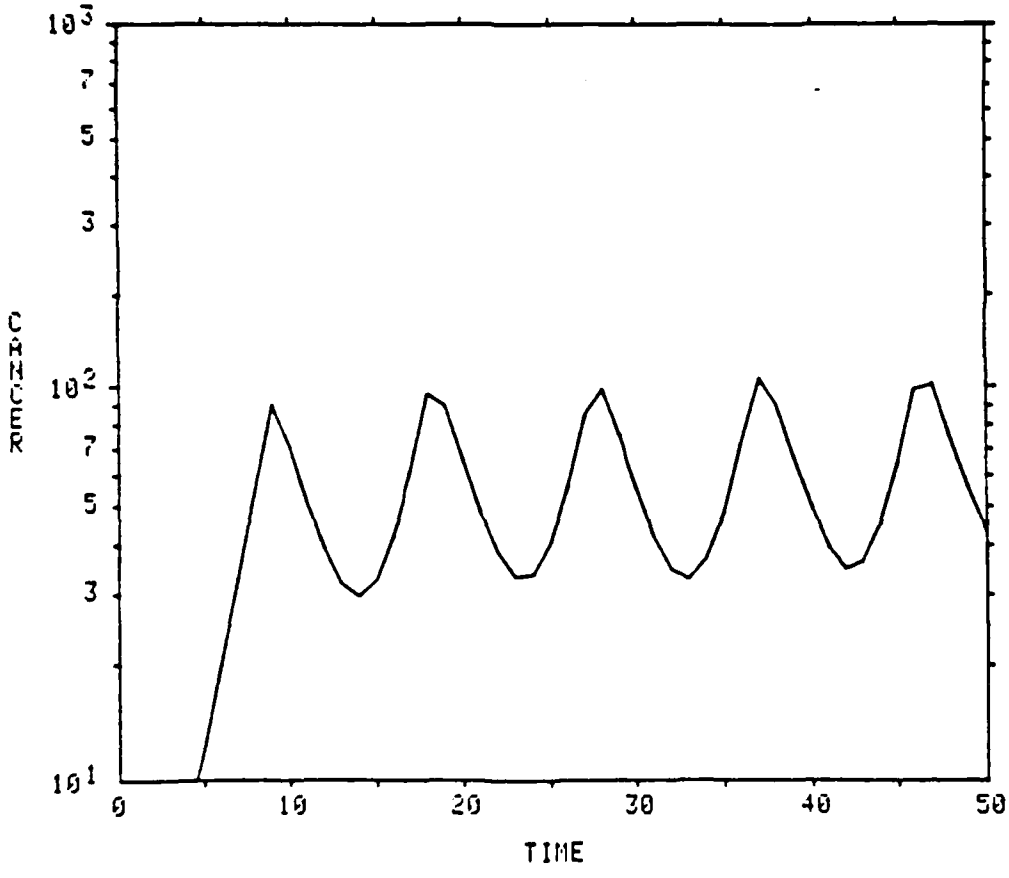
```
2010 LET P=P/C(M,S+2)
2020 WHEN EXCEPTION IN
2030 LET U=(P/NF)^KM*C(M,S+2)
2040 USE
2050 LET U=0
2060 END WHEN
2070 IF M<7 THEN LET C(M+1,S+2)=C(M+1,S+2)+U
2080 IF M<7 THEN LET C(M+1,1)=C(M+1,S+2)
2090 IF M<7 THEN LET C(M+1,S+3)=ST*C(M+1,S+2)
2100 LET C(M,S+2)=C(M,S+2)-U
2110 NEXT M
2120 PRINT#8:T;",";SUM
2130 PRINT T,C(1,S+2),C(2,S+2),C(3,S+2),C(4,S+2)
2140 PRINT " ",C(5,S+2),C(6,S+2),C(7,S+2),SUM
2150 PRINT " ",C(1,S+4) 2160 NEXT T
2170 FOR M=1 TO 9
2180 PRINT#M:"1.E37,1.E37"
2190 NEXT M
2200 REM Q=ST!/(N!*(ST-N)!)
2210 LET SF=1
2220 LET MF=1
2230 FOR X=(ST-N+1) TO ST
2240 LET SF=SF*X
2250 NEXT X
2260 FOR Y=1 TO N
2270 LET MF=MF*Y
```

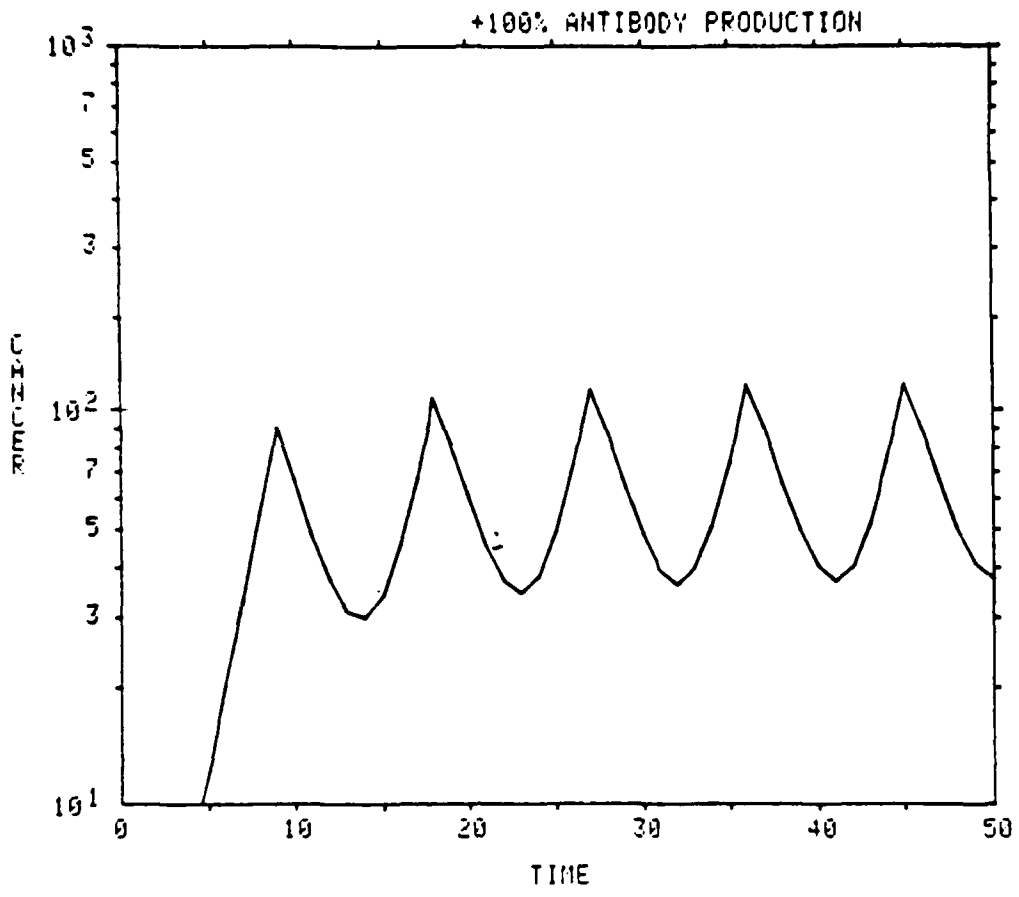
```
2280 NEXT Y
2290 LET Q=SF/MF
2300 RETURN
2310 IF C(M,S+4)>1 THEN PRINT#9:T;",";C(M,S+4)
2320 RETURN
2330 END
```

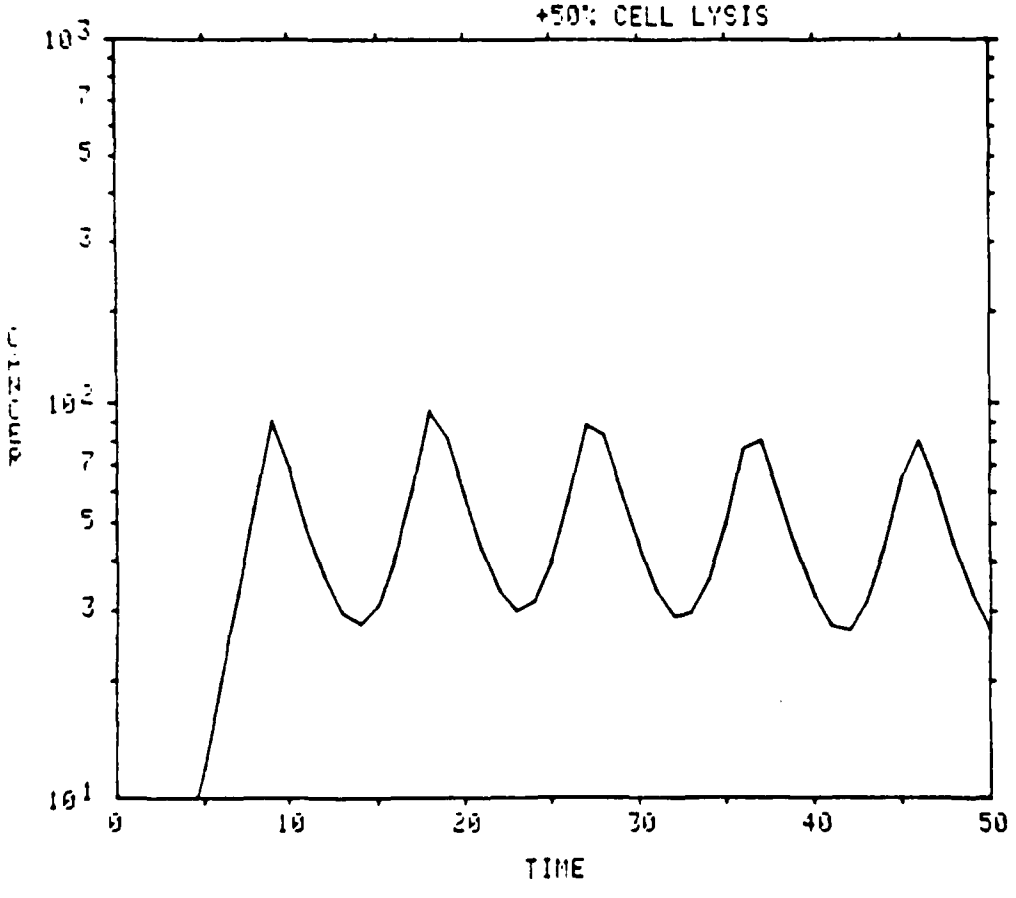
Results

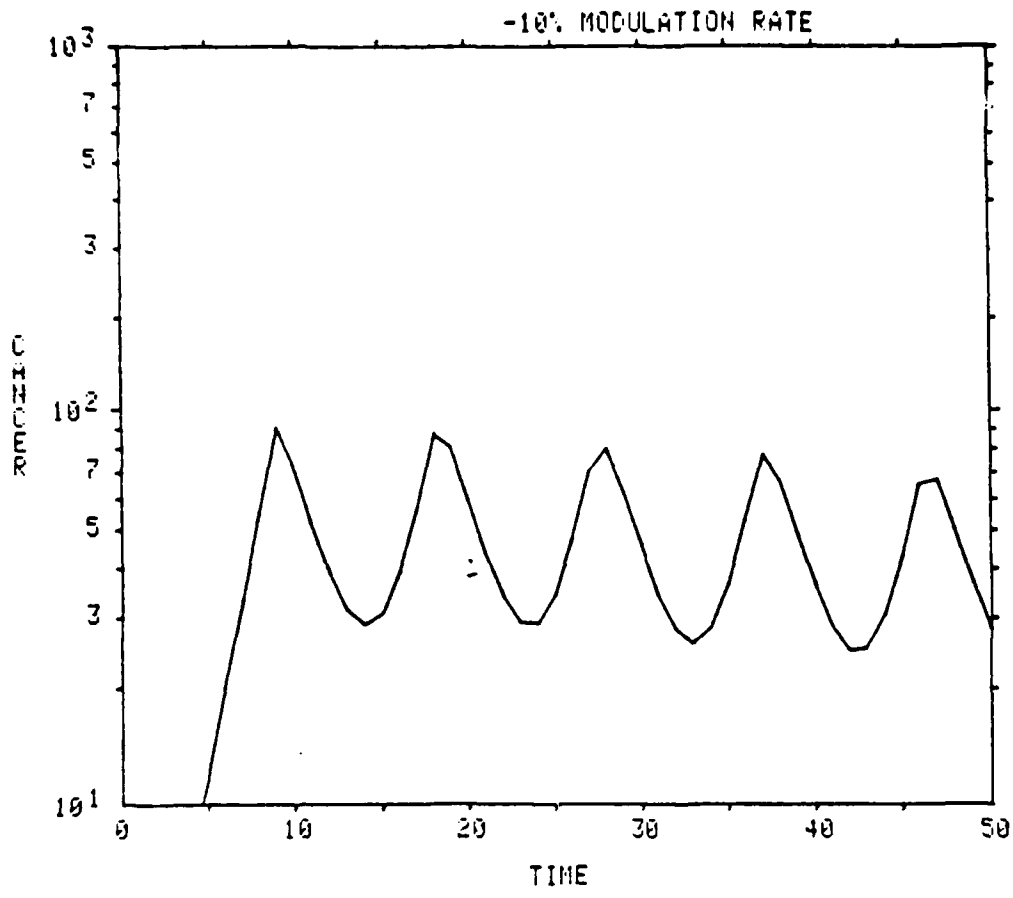
"Steady-State" System

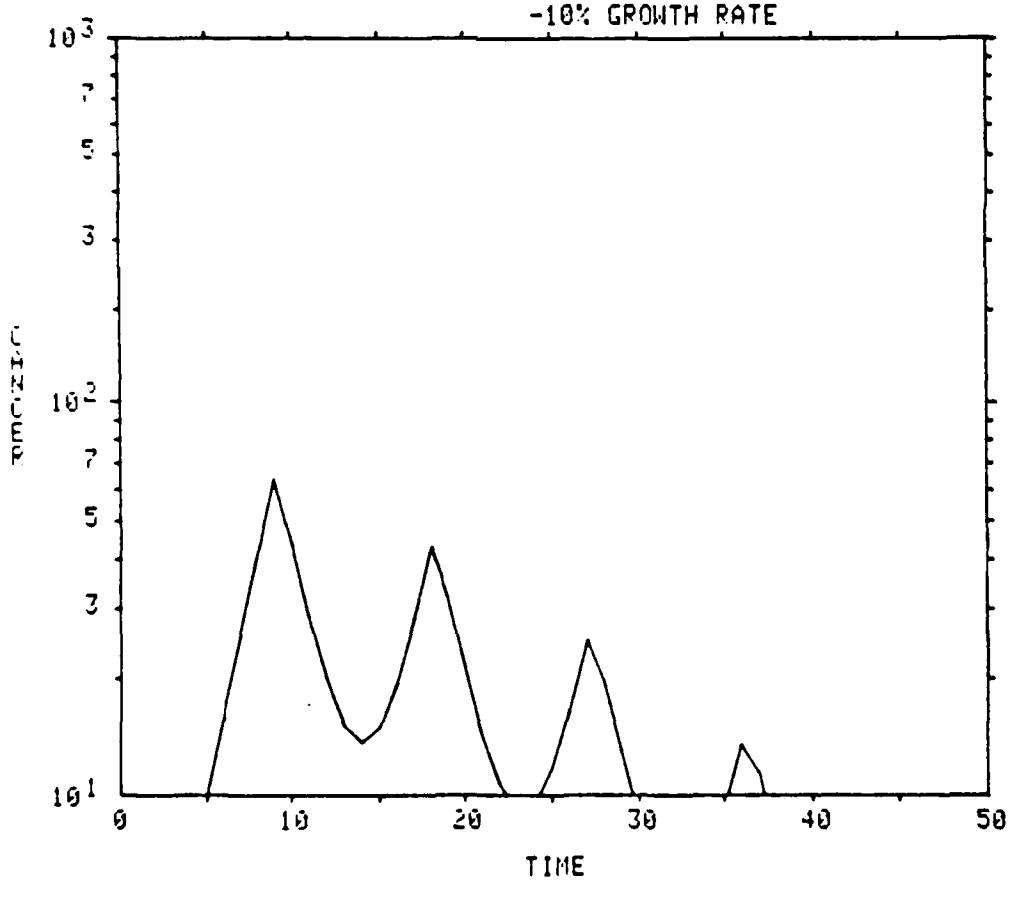
-used as the basis for comparisons of results

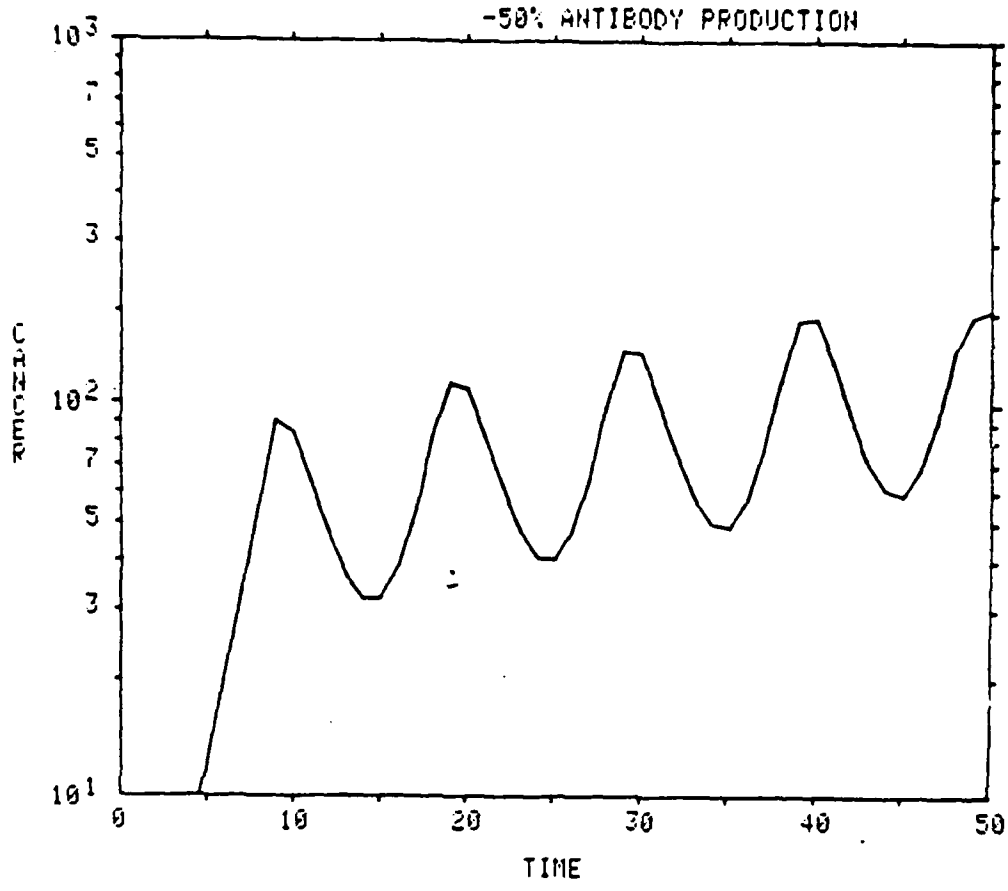


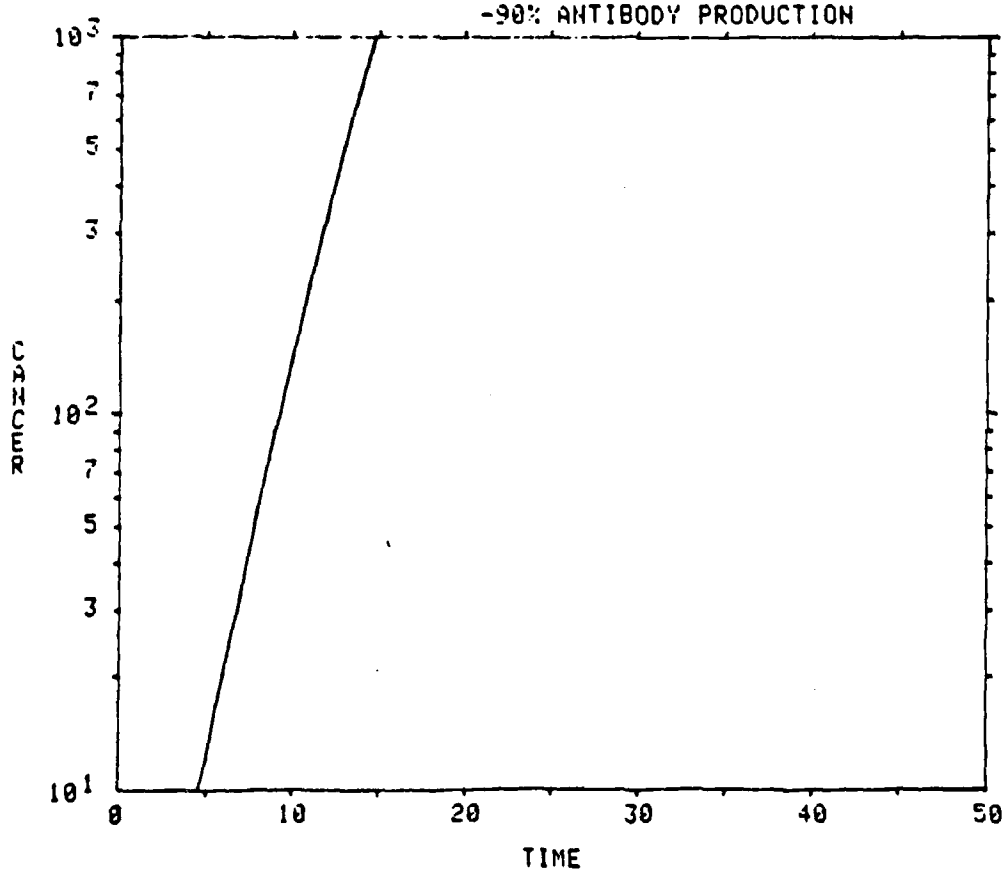

+100% ANTIBODY PRODUCTION
ORGANISMS
10^3
7
5
3
10^2
7
5
3
10^1
0
10
20
30
40
50
TIME


+50% CELL LYSIS
ORGANISMS
10^3
7
5
3
10^2
7
5
3
10^1
0
10
20
30
40
50
TIME


-10% MODULATION RATE
10^3
7
5
3
10^2
7
5
3
10^1
0
10
20
30
40
50
TIME


-10% GROWTH RATE
10^3
7
5
3
10^2
7
5
3
10^1
0
10
20
30
40
50
TIME


-50% ANTIBODY PRODUCTION
CANCER
10^3
7
5
3
10^2
7
5
3
10^1
0
10
20
30
40
50
TIME


-90% ANTIBODY PRODUCTION
CANCER
10^3
7
5
3
10^2
7
5
3
10^1
0
10
20
30
40
50
TIME

END

DTIC

10-86